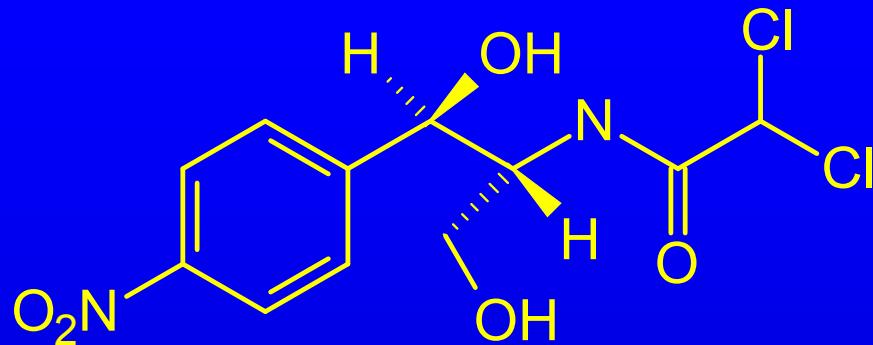


Developmental Pharmacology

Scaling adult doses to infants based on body weight or surface area does not account for developmental changes that affect drug disposition or tissue/organ sensitivity.

**Frank Balis, M.D.
February 19, 2009**

Chloramphenicol



- Natural product of *Streptomyces* (1947)
- Inhibits protein synthesis (bacteriostatic)
- Eliminated by glucuronide conjugation (90%) and renal excretion (<10%)
- Nursery infections treated with high doses

Chloramphenicol in Infants

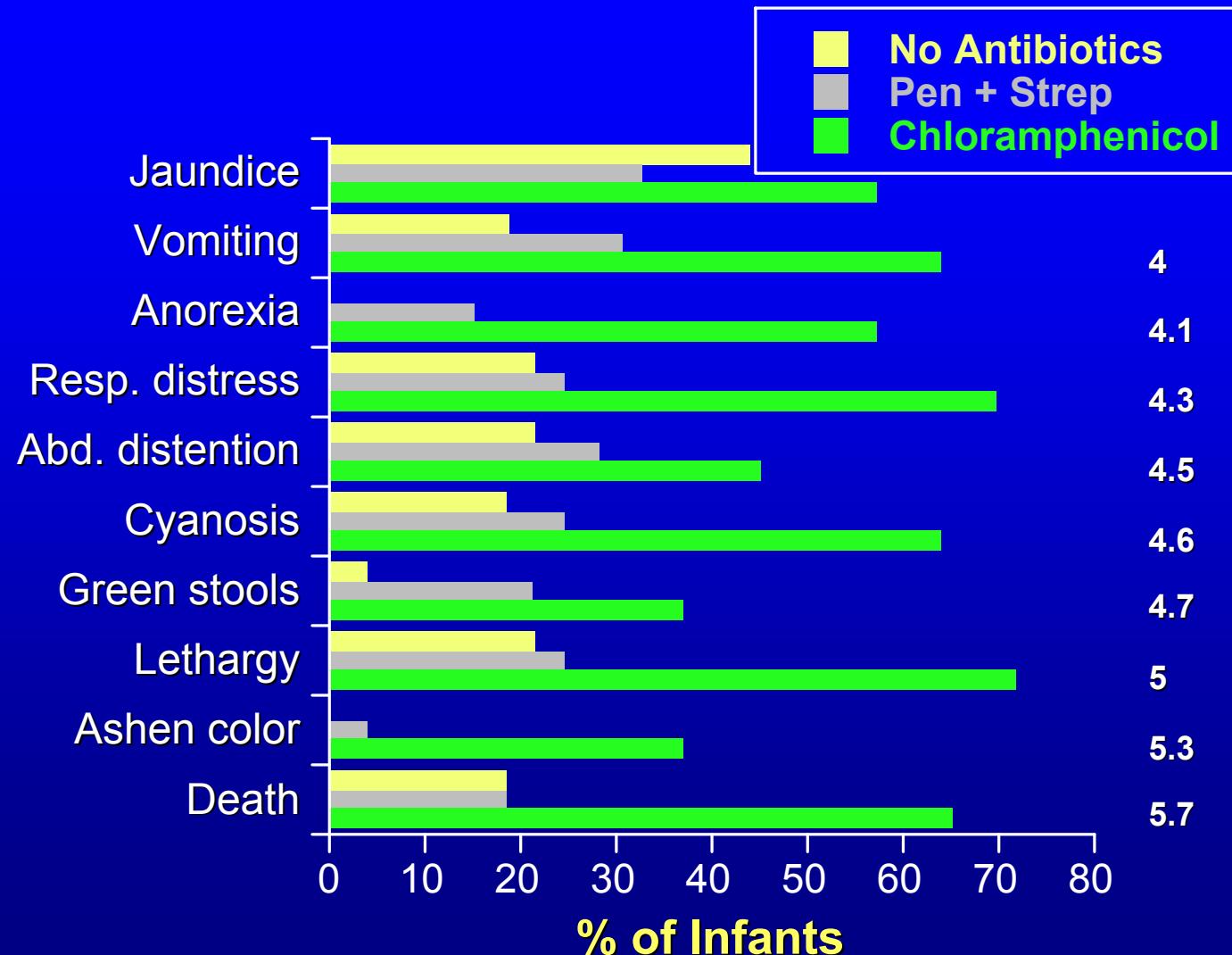
- **3320 gm infant, 44 week gestation**
- **Meconium stained, foul smelling, timing of ROM unknown**
- **Procaine penicillin (50,00 units) + chloramphenicol (250 mg) IM q8h - 230 mg/kg/day x 72 hr**
- **Day 4, gray color & cold, moist skin**
- **Died at 106 hr, 8 hr after onset of vascular collapse**

Chloramphenicol in Premature Infants

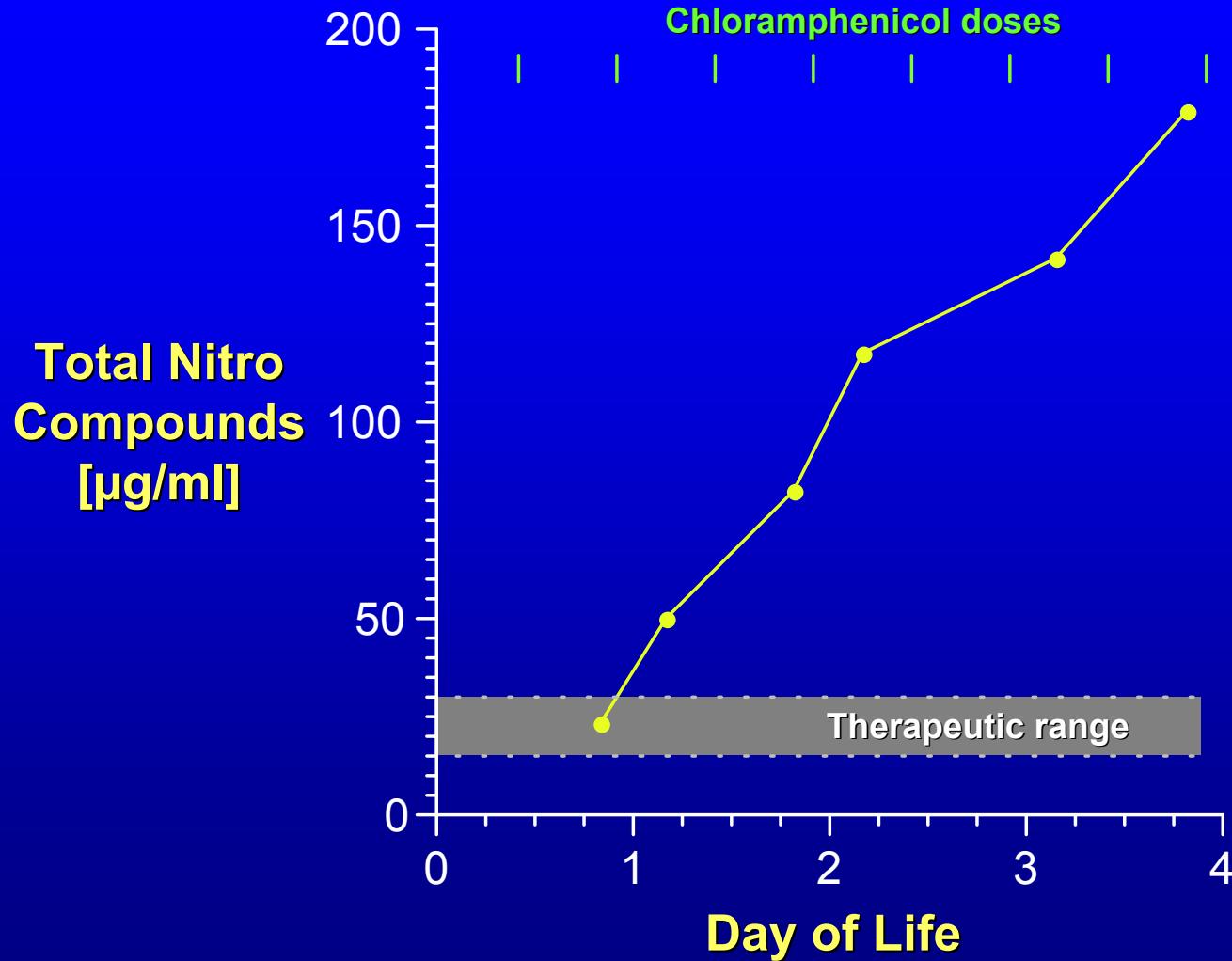
Premature infants born ≥ 24 hrs after ROM

	All Infants		2001-2500 gm	
	n	Deaths	n	Deaths
No antibiotics	32	6	17	1
Pen + strep	33	6	24	0
Chloramphenicol	30	19	16	8
Pen + strep + chloramphenicol	31	21	15	6

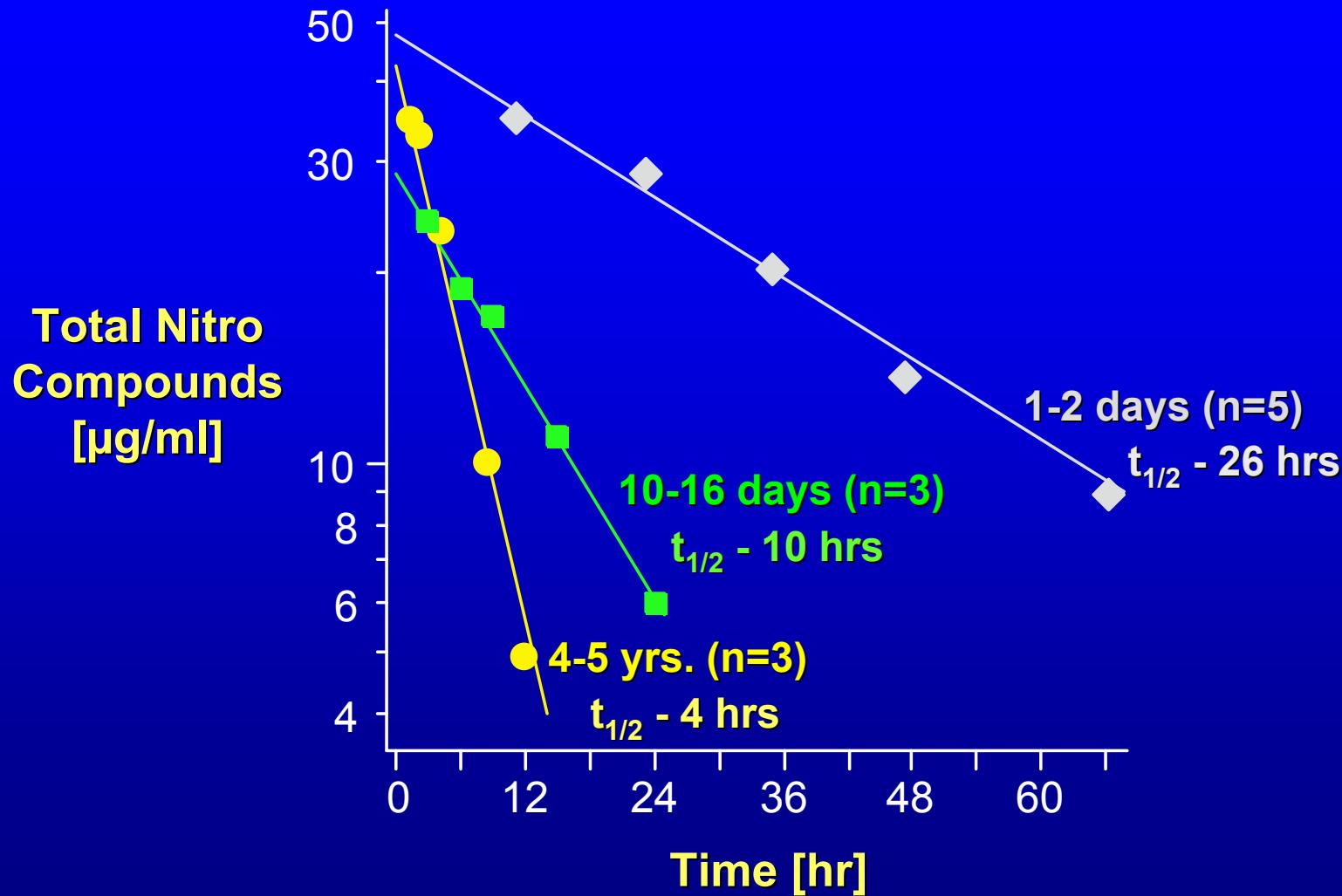
Gray Baby Syndrome



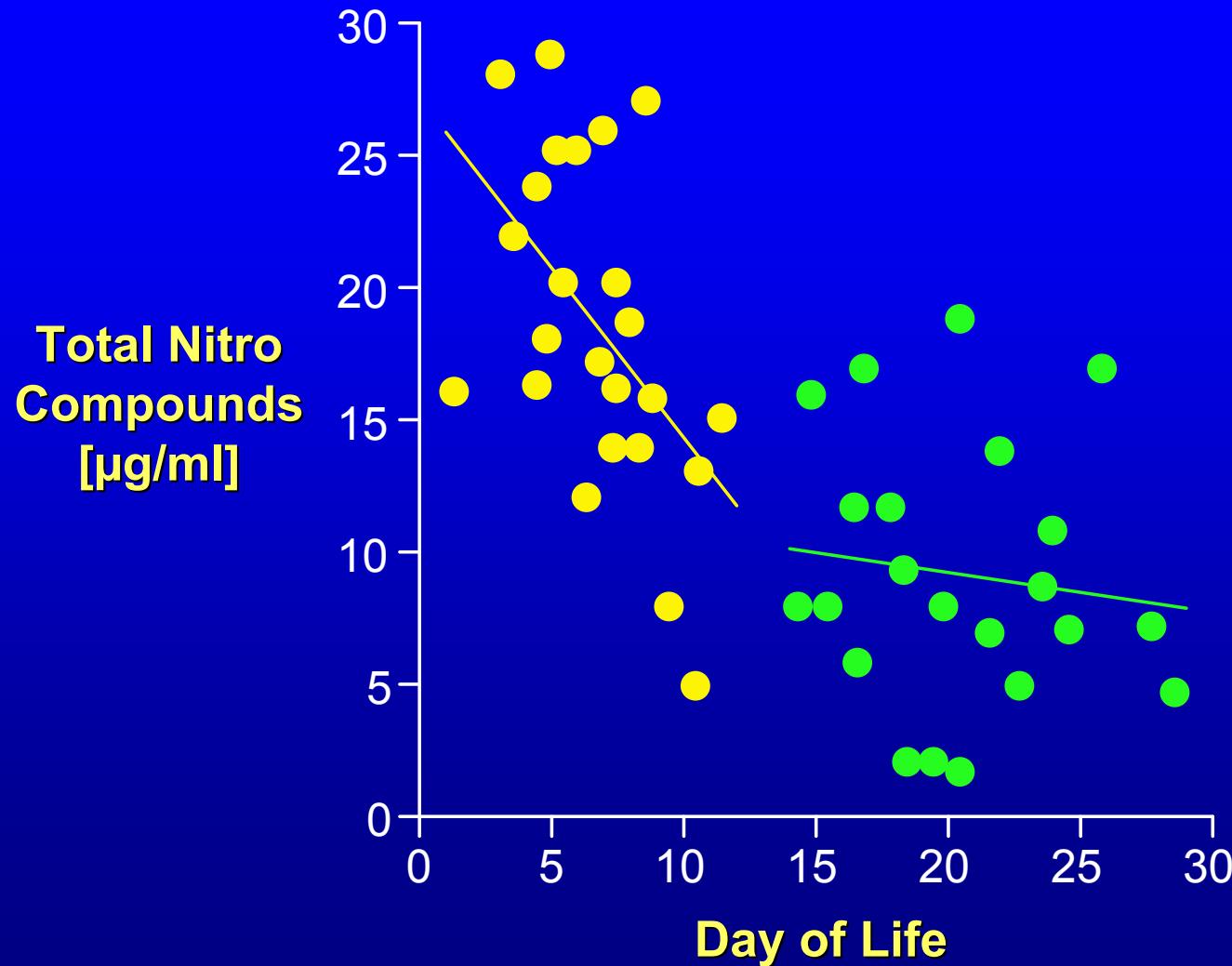
Chloramphenicol Blood Levels



Chloramphenicol Pharmacokinetics



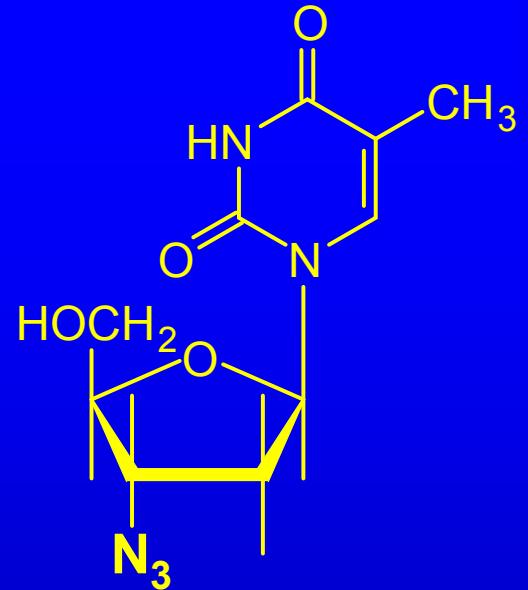
Repeated Administration



Drug Use in Infants and Children

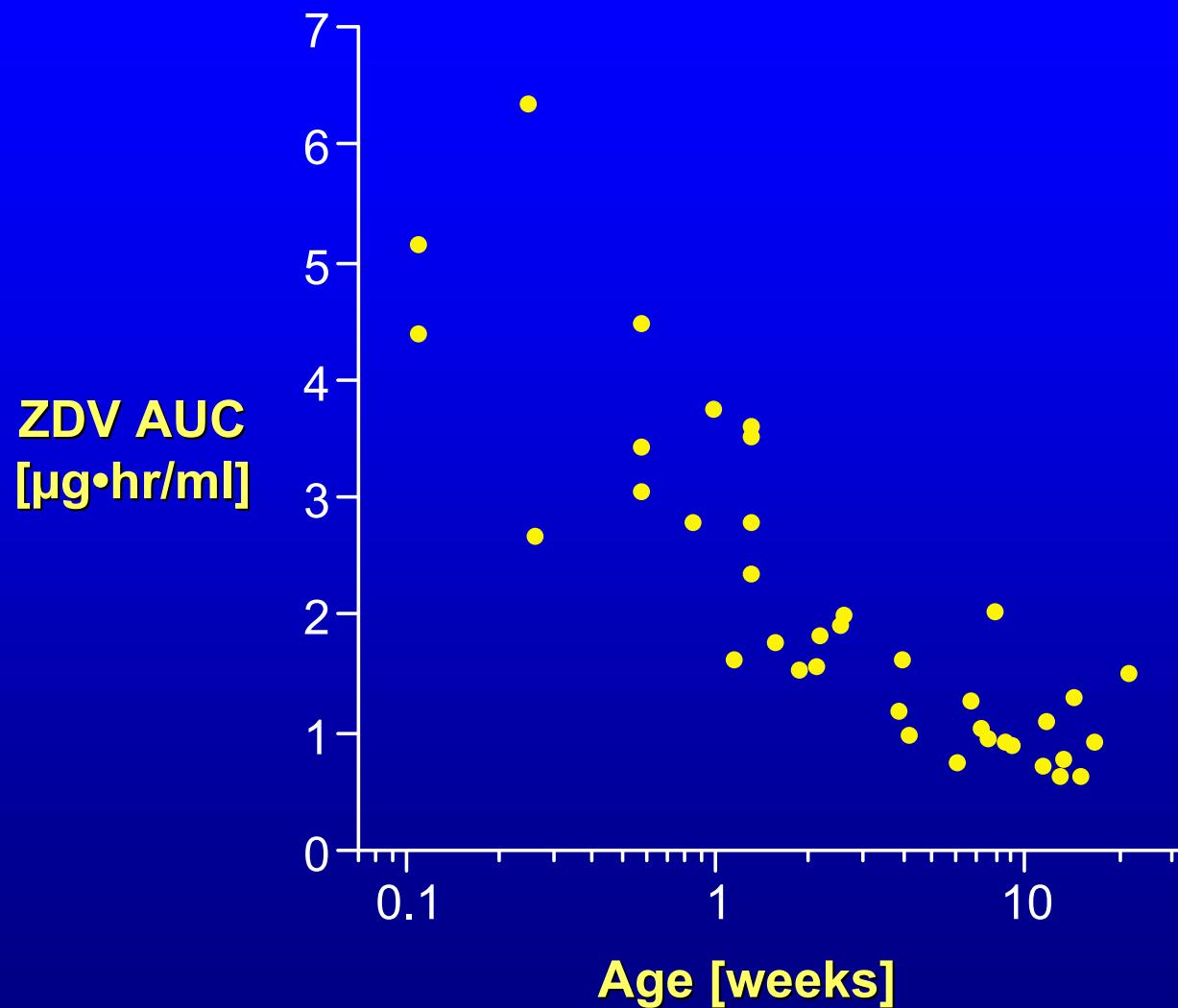
- **Scaling adult doses based on body weight or surface area does not account for developmental changes that affect drug disposition or tissue/organ sensitivity.**
- **Pharmacologic impact of developmental changes are often discovered when unexpected or severe toxicity in infants and children leads to detailed pharmacologic studies.**
- **Therapeutic tragedies could be avoided by performing pediatric pharmacologic studies during the drug development process (before wide-spread use of agents in infants and children).**

Zidovudine



- Synthetic nucleoside analog
- Inhibits HIV reverse transcriptase
- Eliminated by glucuronide conjugation (67%) and renal excretion (33%)
- Perinatal therapy to prevent HIV transmission

Zidovudine in the Newborn



Zidovudine in Newborns

Group	Age (days)	Clearance (ml/min/kg)	$t_{1/2}$ (hr)	F (%)
Preterm	5.5	2.5	7.2	
	17.7	4.4	4.4	
Term	^ 14	10.9	3.1	
	>14	19.0	1.9	

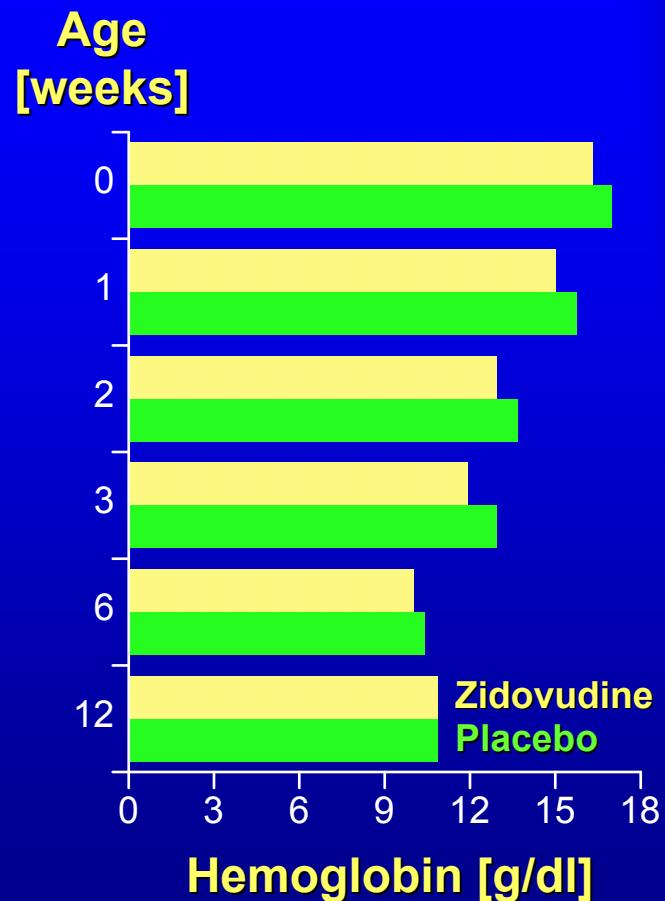
Age Group	Clearance (ml/min/kg)	$t_{1/2}$ (hr)	F (%)
1-13 yrs	24	1.5	68
Adults	21	1.1	63

Prevention of Vertical Transmission

- Randomized, double-blind, placebo controlled trial
- Rate of vertical transmission was the primary endpoint
- Zidovudine/placebo regimen
 - Mothers: 100 mg of ZDV antepartum orally, 5 times daily, and then continuous infusion of 1 mg/kg/hr during labor and delivery
 - Infants: 2 mg/kg orally every 6 hours for 6 weeks, beginning 8-12 hours after birth.

Prevention of HIV Transmission

	Zidovudine	Placebo
AGE >32 WEEKS		
Number	121	127
HIV-infected	9	31
Rate (%)	7.4	24.4
AGE \leq 1 YEAR		
Number	83	89
HIV-infected	7	20
Rate (%)	8.4	22.5



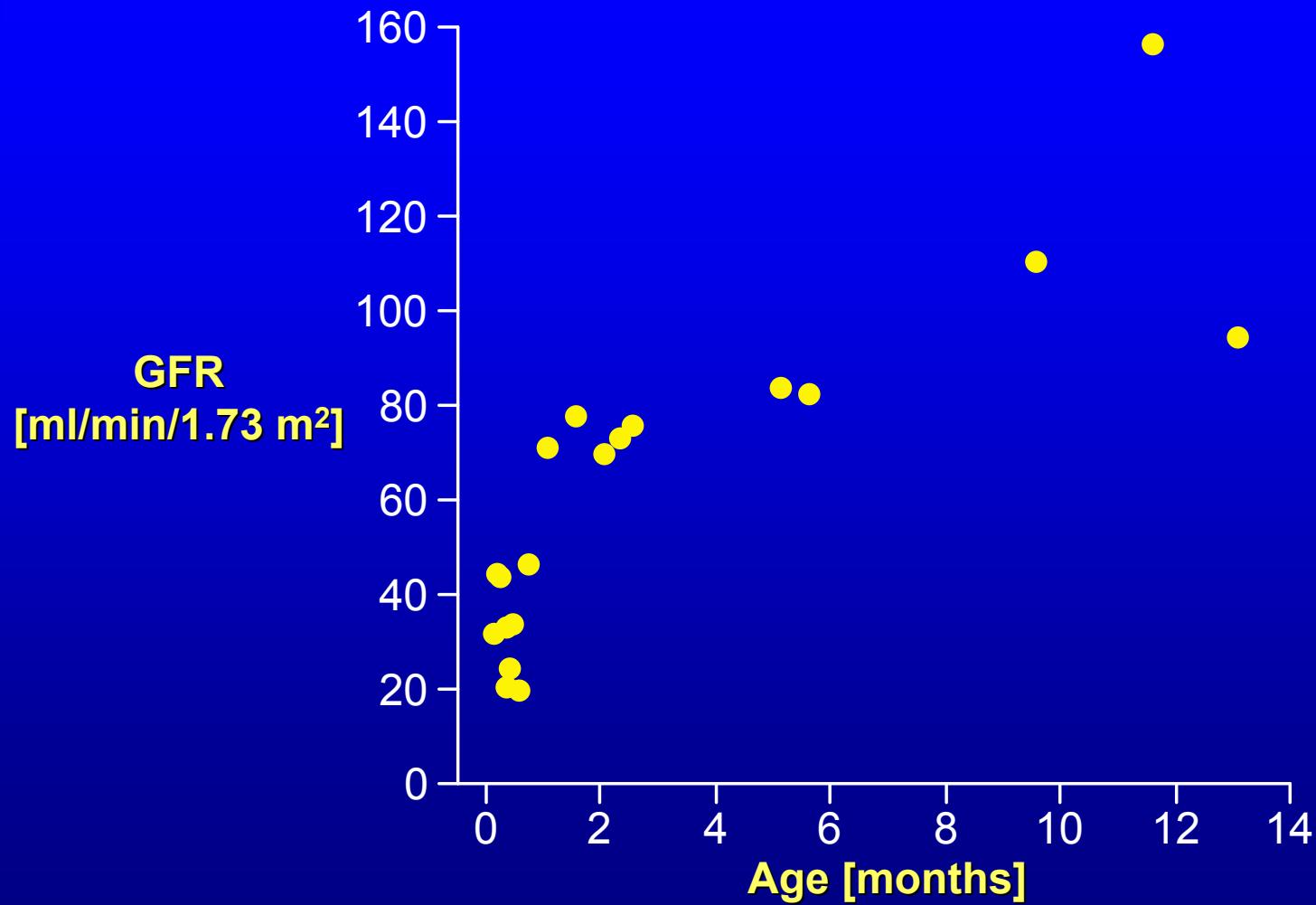
Ontogeny and Pharmacology

- **Excretory organ (liver and kidneys) development has the greatest impact on drug disposition (pharmacokinetics)**
- **The most dramatic changes occur during the first days to months of life**
- **Anticipate age-related differences in drug disposition based on knowledge of ontogeny**
- **Effect of ontogeny on tissue/organ sensitivity to drugs (pharmacodynamics) is poorly studied**
- **Disease states may alter a drug's PK/PD**

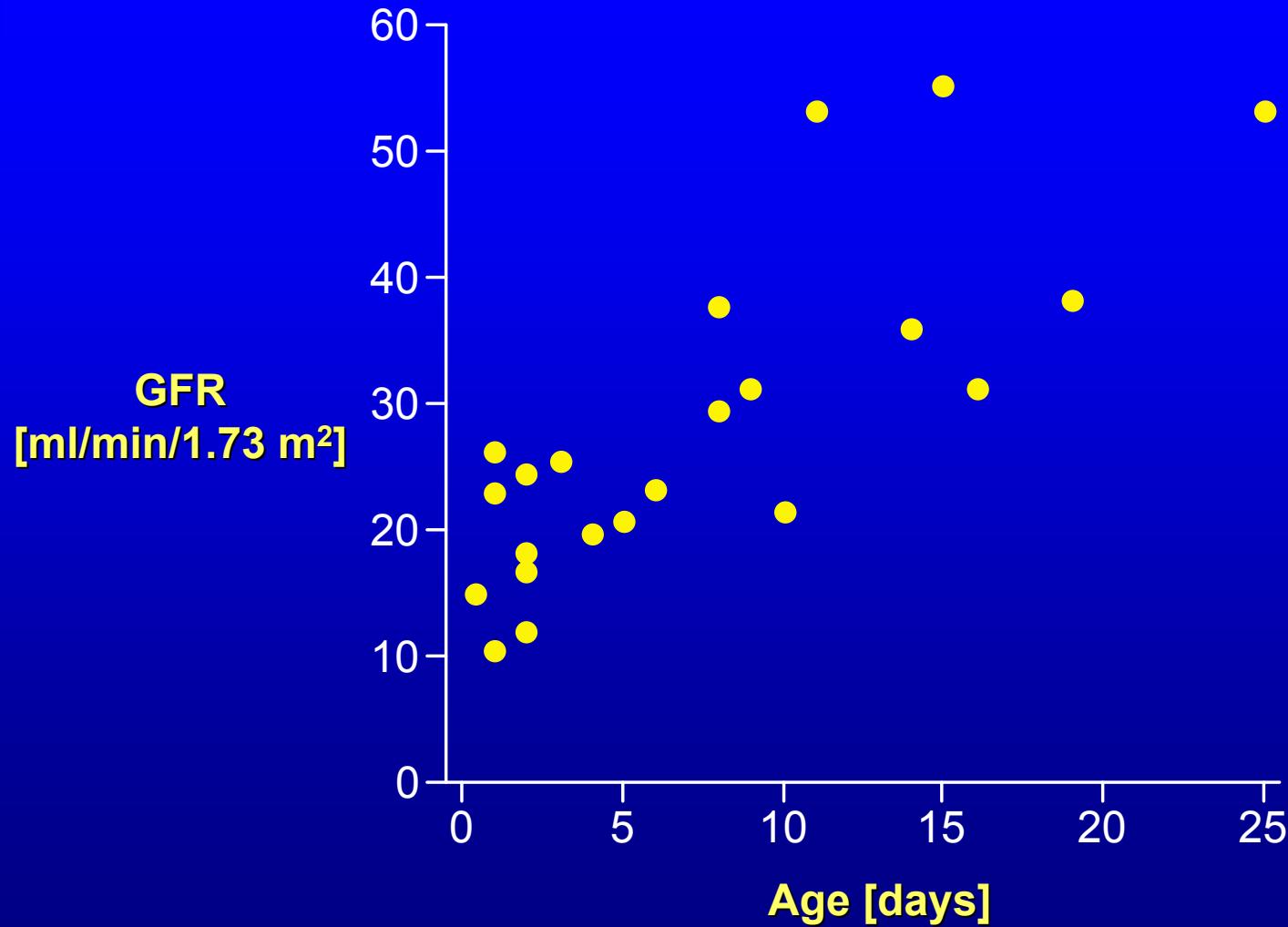
Renal Ontogeny

- **Glomerular filtration rate**
 - Low at birth
 - Full term newborn - 10-15 ml/min/m²
 - Premature - 5-10 ml/min/m²
 - GFR doubles by 1 week of age
 - Adult values by 6-12 months of age
- **Tubular function**
 - Secretory function impaired at birth
 - Glomerulotubular imbalance
 - Adult values by 1 year of age

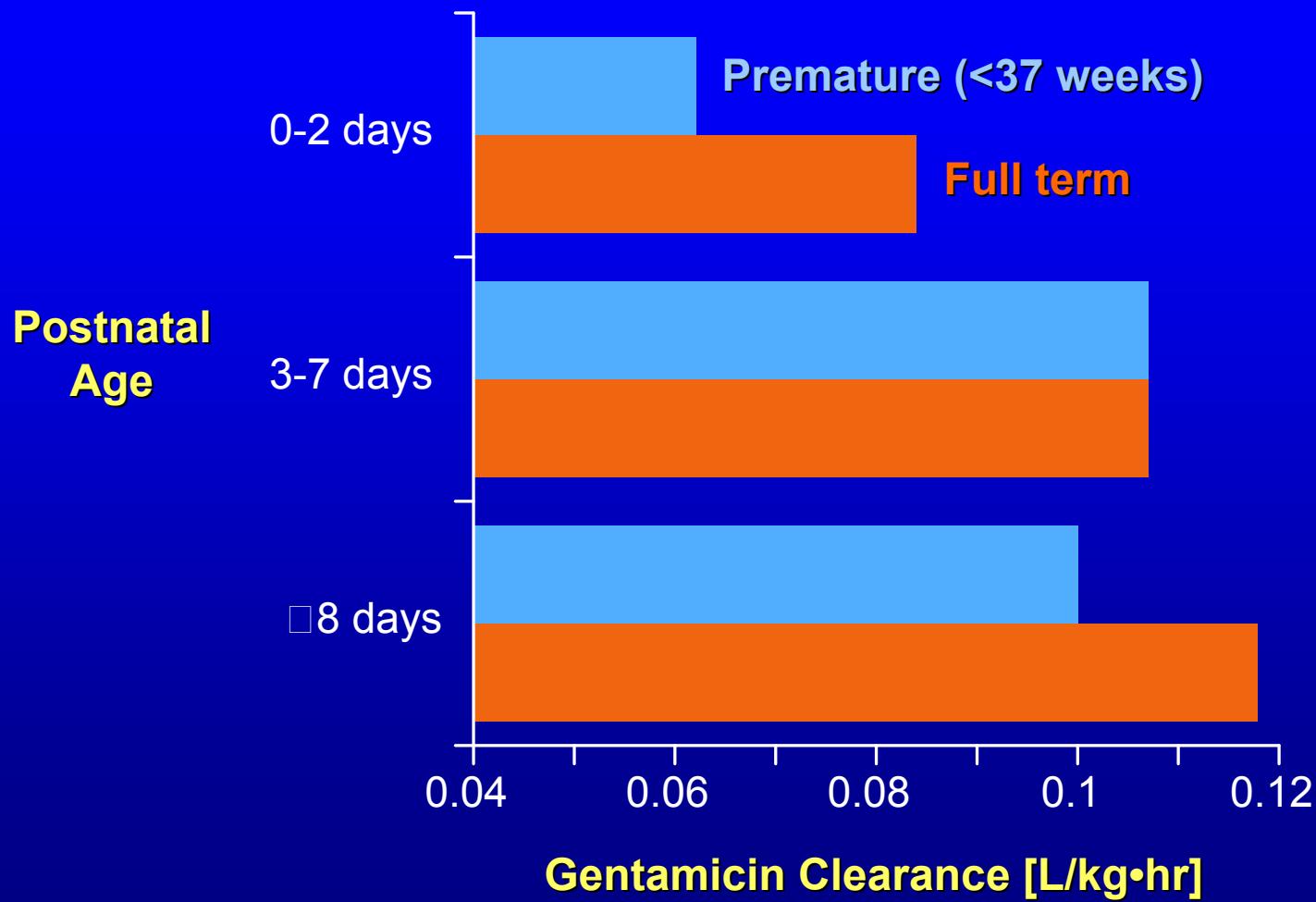
Glomerular Filtration Rate



GFR in Infants



Gentamicin Clearance

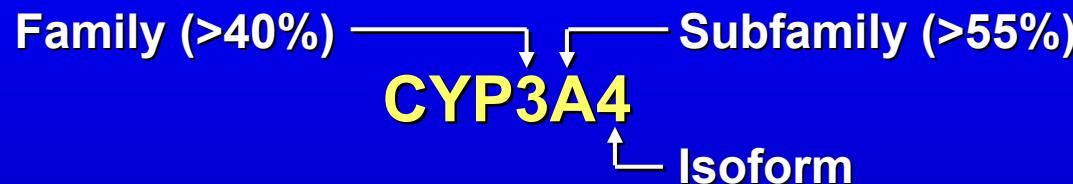


Hepatic Ontogeny

- Phase 1 (oxidation, hydrolysis, reduction, demethylation)
 - Activity low at birth
 - Mature at variable rates
 - Oxidative metabolism increases rapidly after birth
 - Alcohol dehydrogenase reaches adult levels at 5 yrs
 - Activity in young children exceeds adult levels
- Phase 2 (conjugation, acetylation, methylation)
 - Conjugation:
 - Glucuronidation ↓ at birth
 - Sulfatation ↑ at birth
 - Acetylation ↓ at birth, “fast” or “slow” phenotype by 12-15 mo.

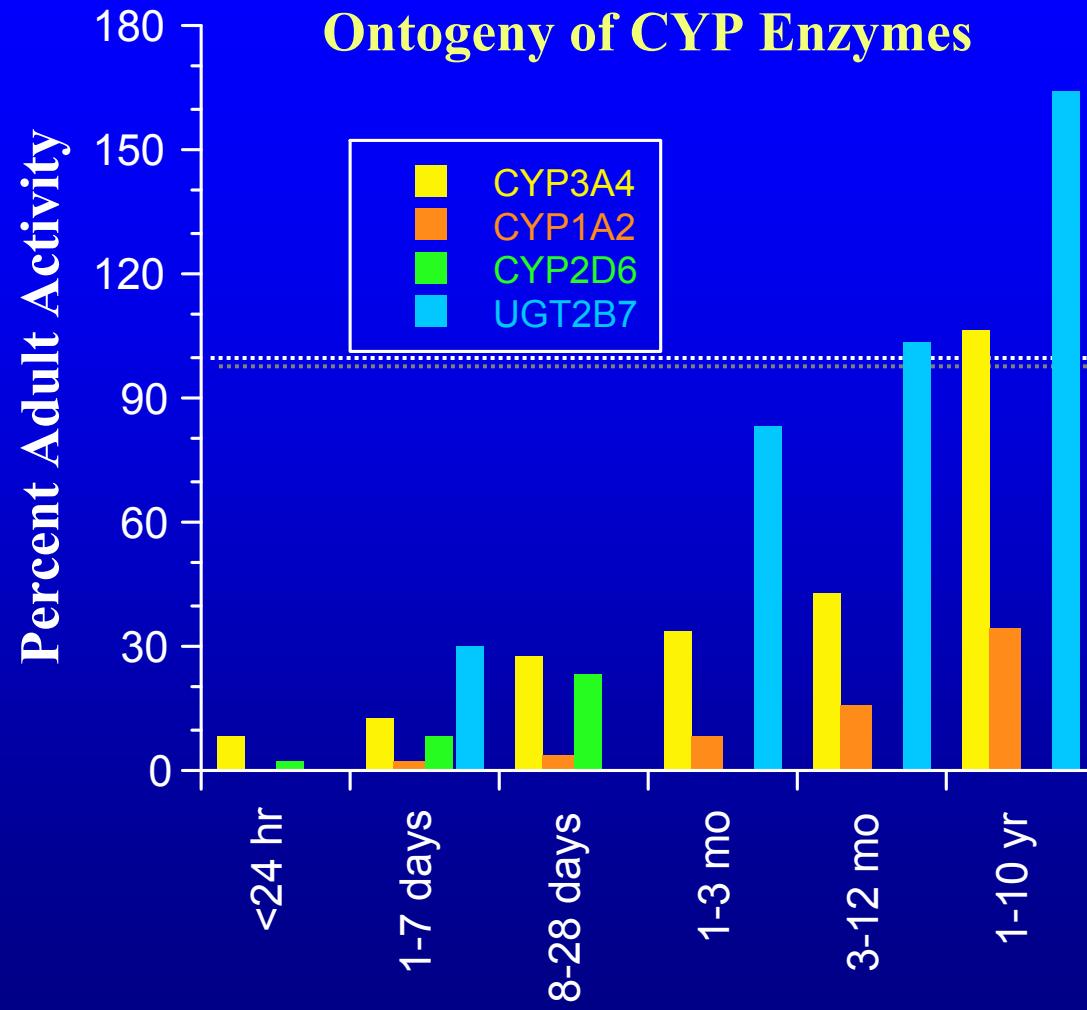
Cytochrome P450 (CYP) Enzymes

- Superfamily of Phase 1 enzymes (oxidation, demethylation)
- Nomenclature:

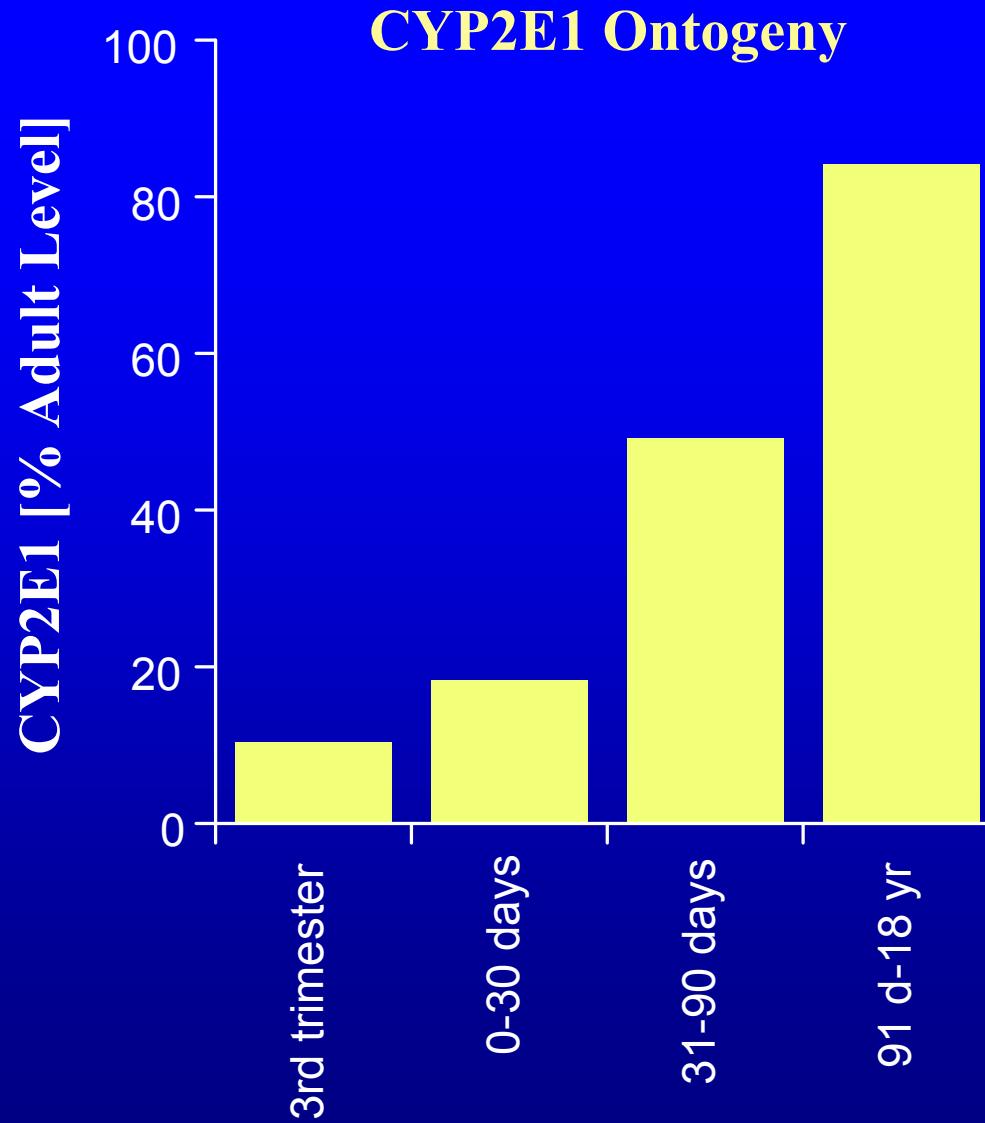


- 17 Families and 39 subfamilies in humans
- CYP1, CYP2, CYP3 are primary drug metabolizing enzymes
- Half of all drugs metabolized by CYP3A subfamily
- CYP3A4 is most abundant hepatic P450 enzyme and metabolizes at least 50 drugs

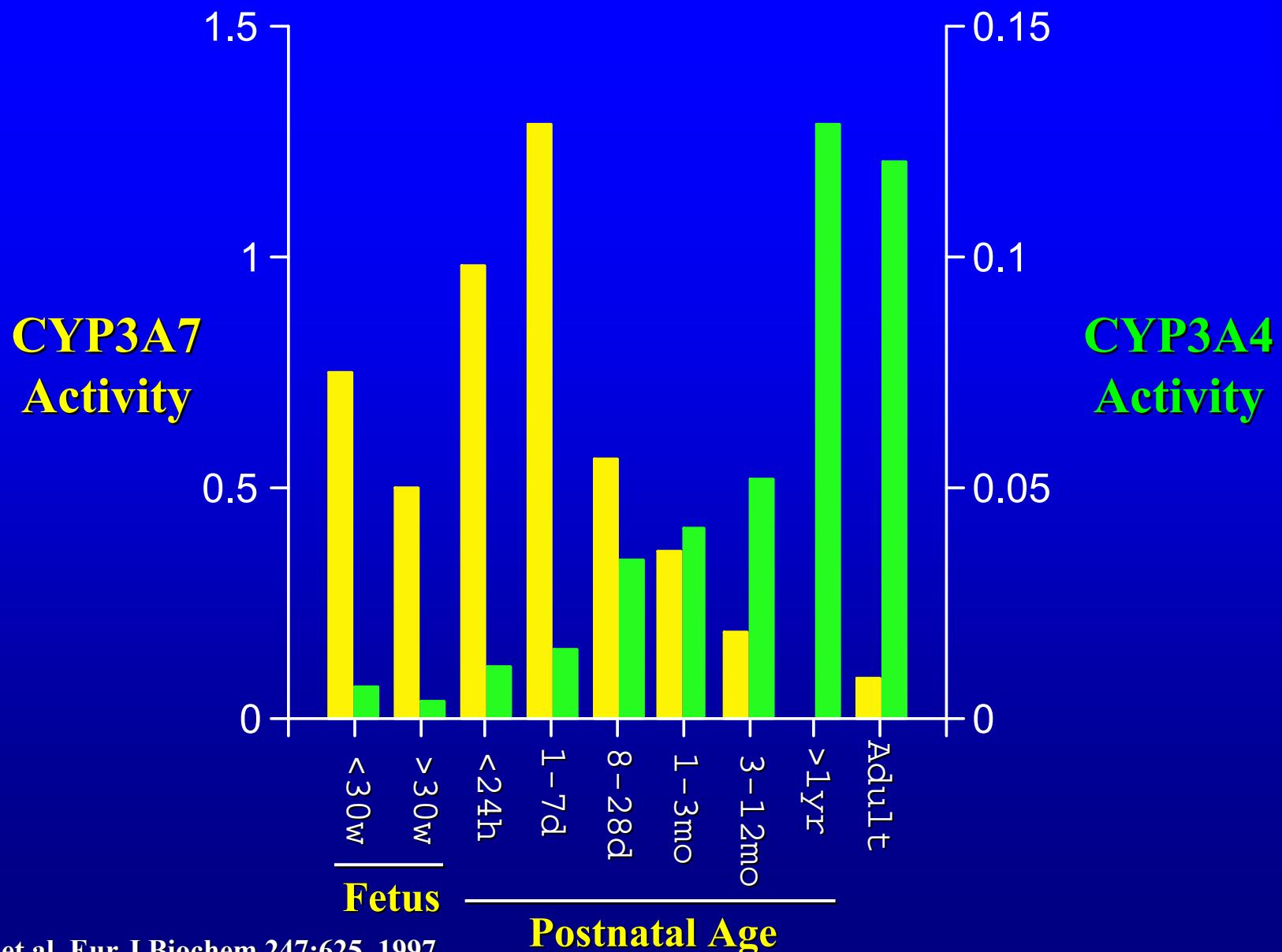
CYP Ontogeny



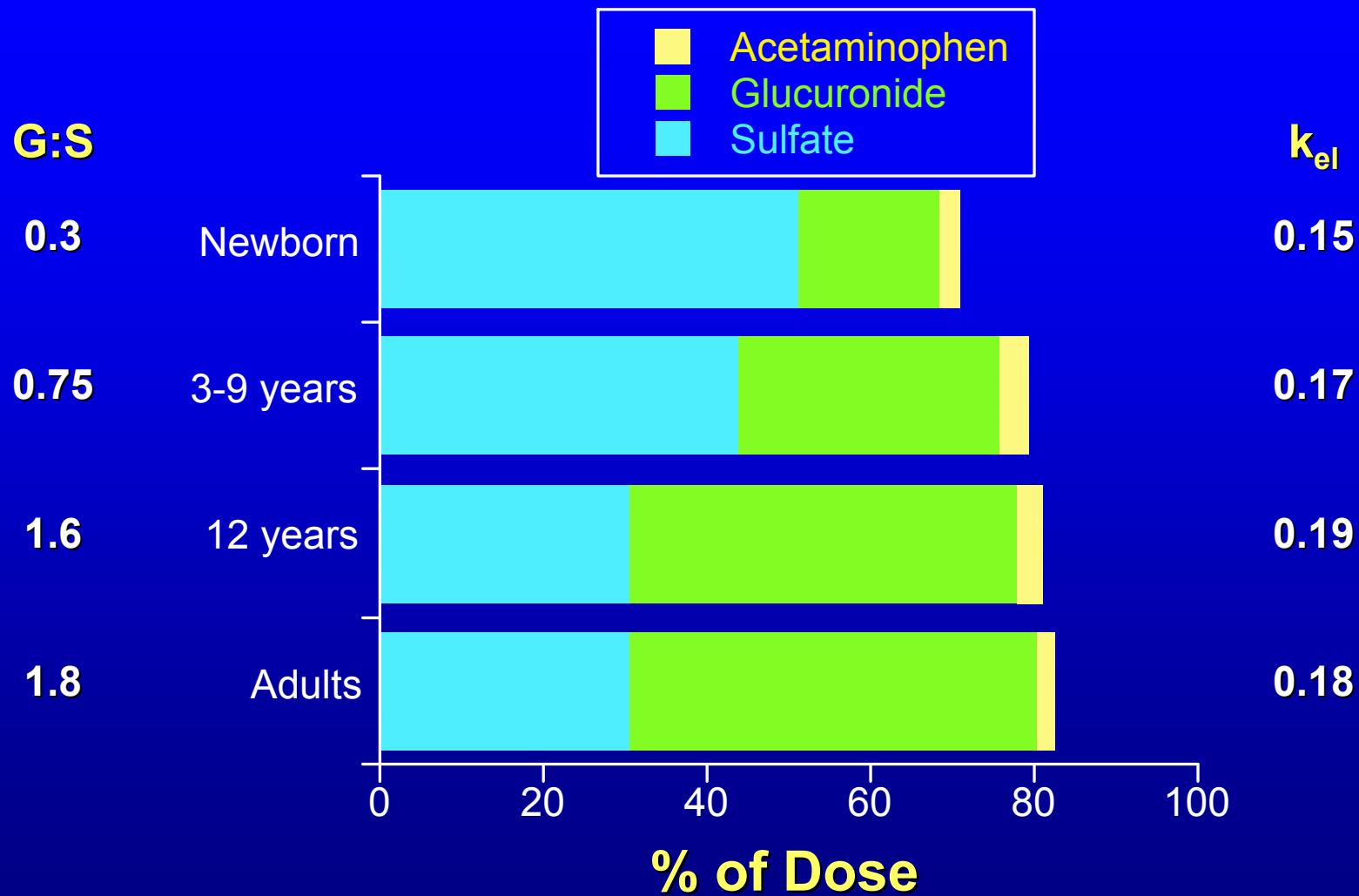
CYP2E1 Ontogeny



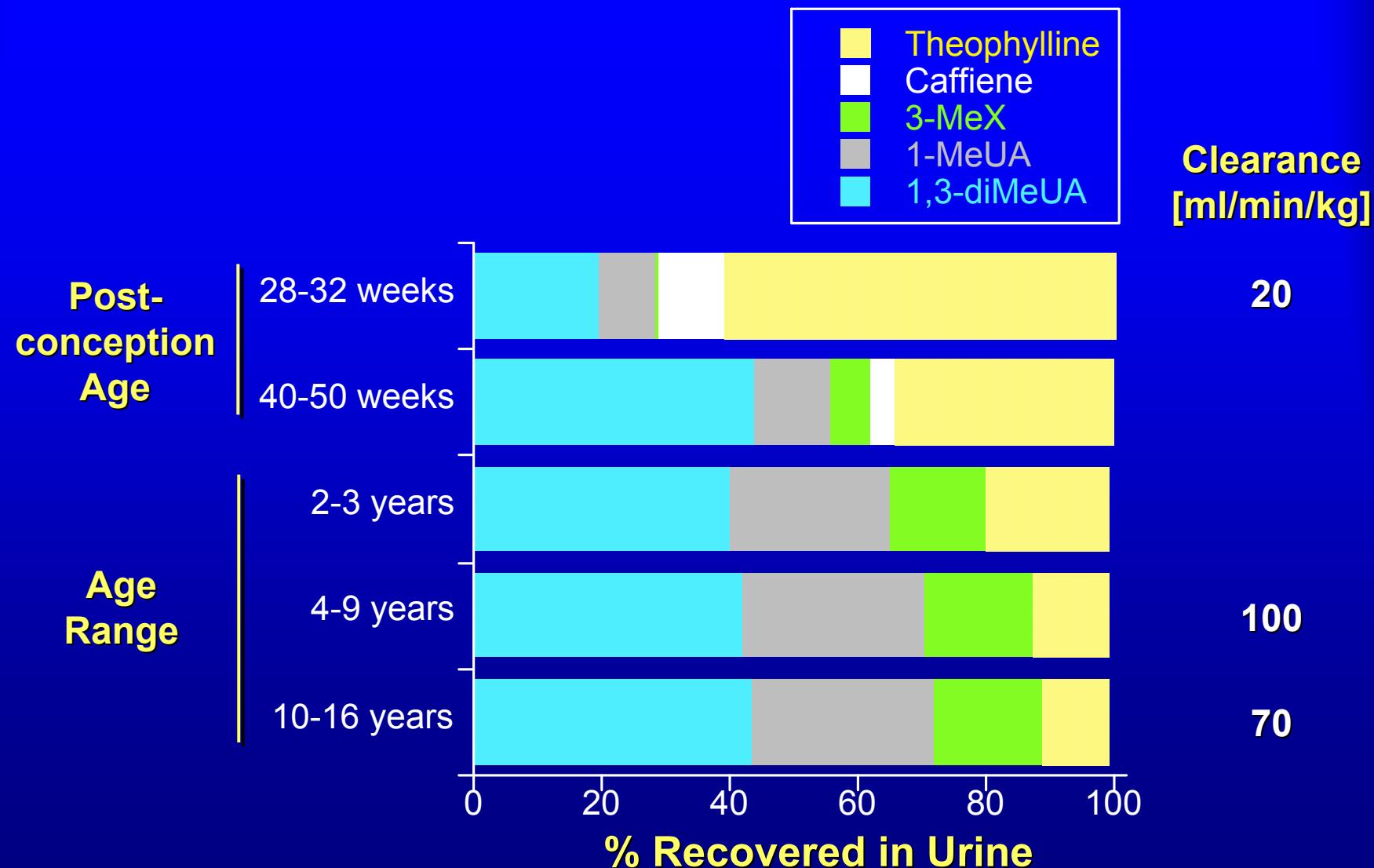
CYP3A Ontogeny



Acetaminophen Metabolism



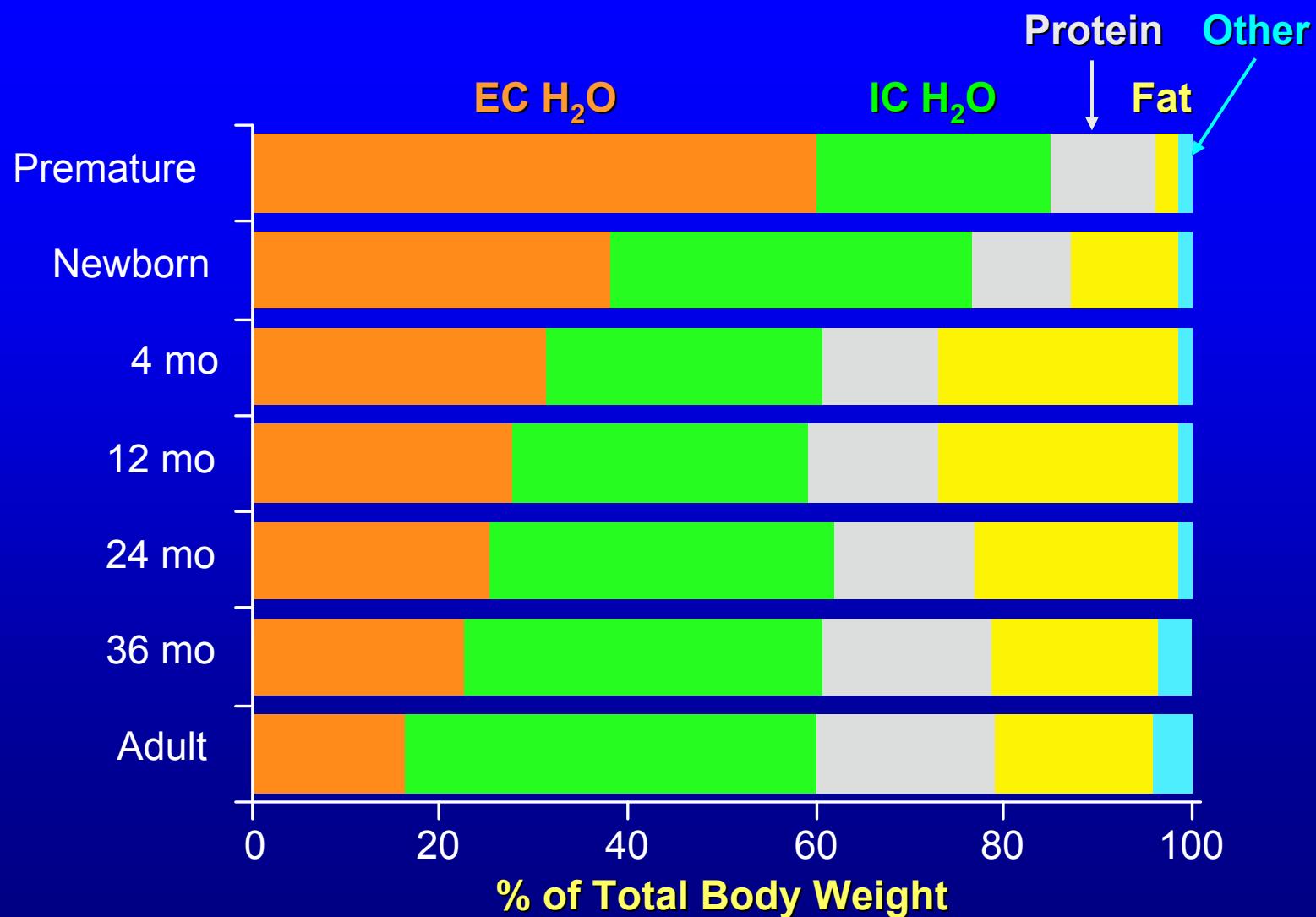
Theophylline Urinary Metabolites



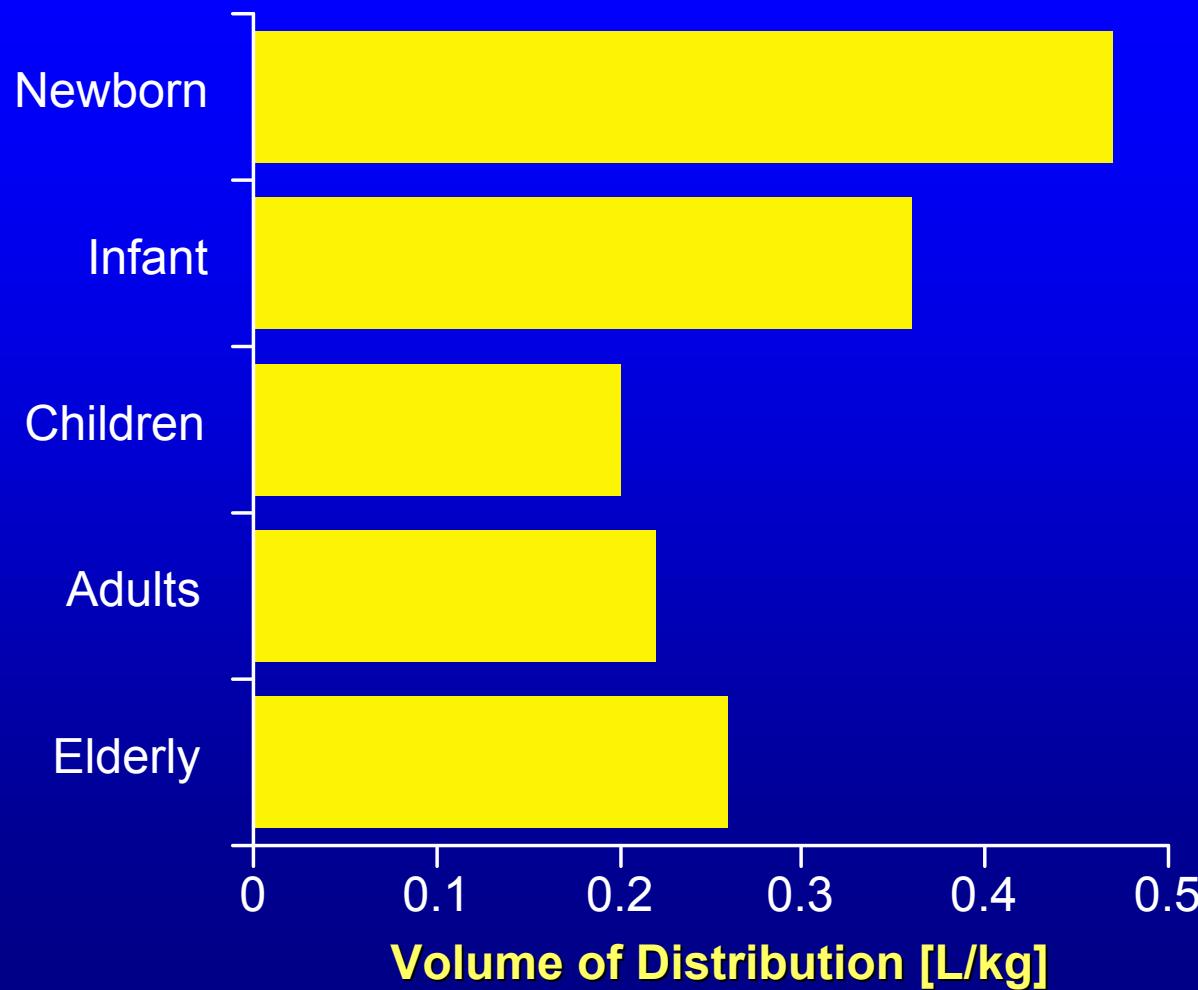
Factors Affecting Drug Distribution

- Physicochemical properties of the drug
- Cardiac output/Regional blood flow
- Degree of protein/tissue binding
- Body composition
 - Extracellular water
 - Adipose tissue

Ontogeny of Body Composition



Volume of Distribution of Sulfa



Tissue and Organ Weight

	% of Total Body Weight		
	Fetus	Newborn	Adult
Skeletal muscle	25	25	40
Skin	13	4	6
Skeleton	22	18	14
Heart	0.6	0.5	0.4
Liver	4	5	2
Kidneys	0.7	1	0.5
Brain	13	12	2

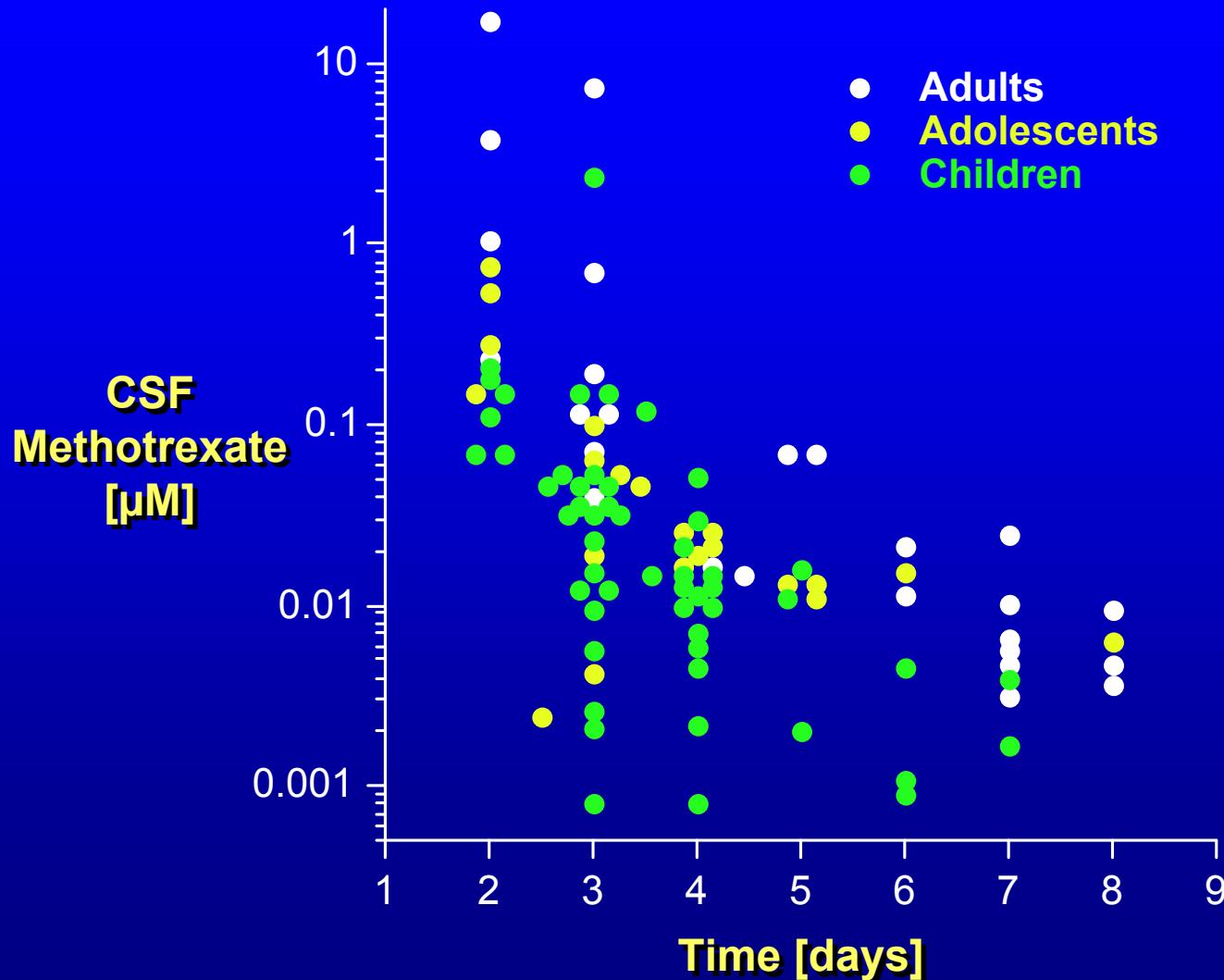
Plasma Proteins

	Change from Adult Values		
	Newborn	Infant	Child
Total protein	↓	↓	=
Albumin	↓	=	=
α_1-Acid glycoprotein	↓		=
Fetal albumin	Present	Absent	Absent
Globulin	↓	↓	=

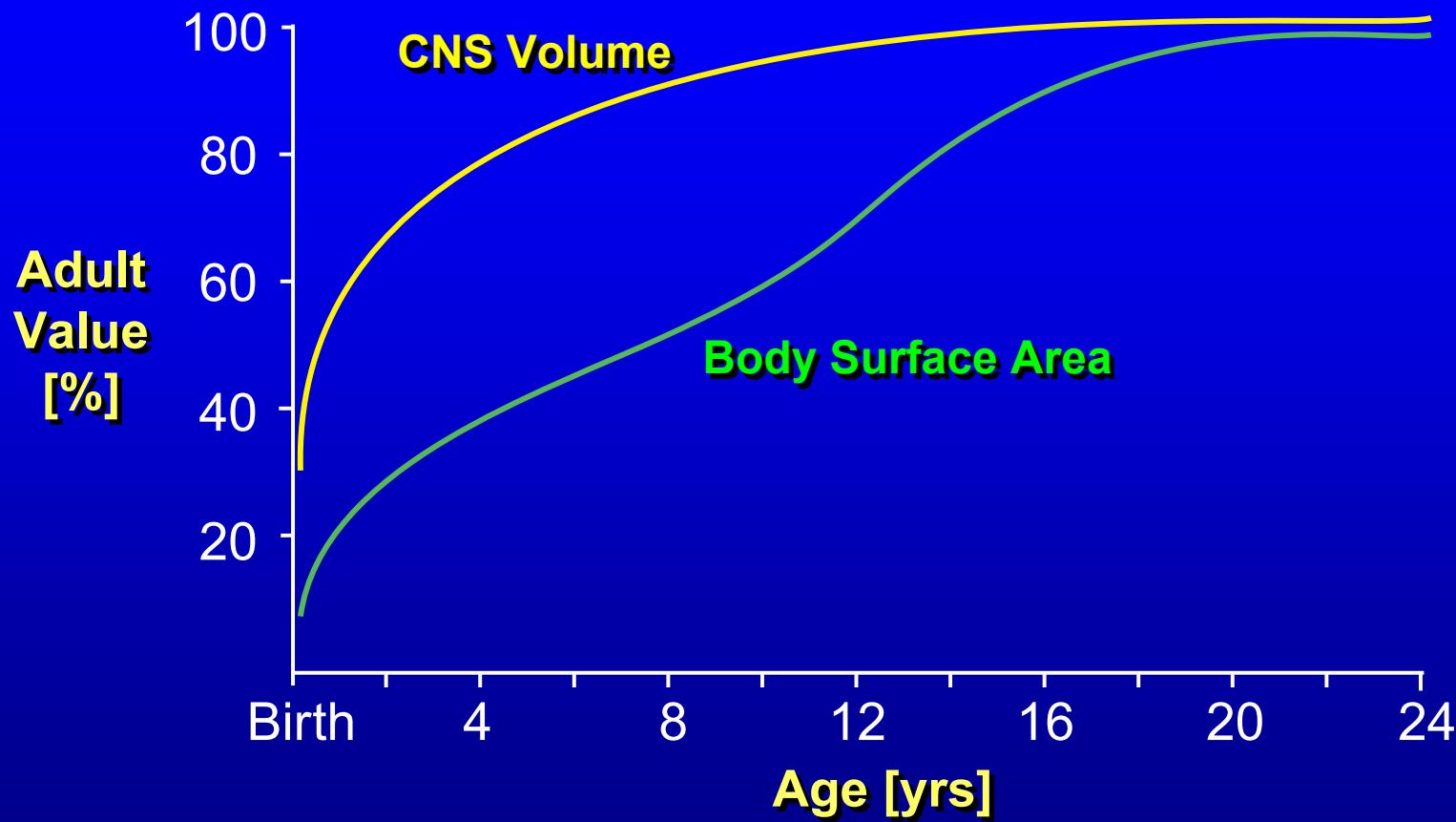
Protein Binding in Cord and Adult Plasma

	Plasma Protein Binding (%)	
	Cord	Adult
Acetominophen	36.8	47.5
Chloramphenicol	31	42
Morphine	46	66
Phenobarbital	32.4	50.7
Phenytoin	74.4	85.8
Promethazine	69.8	82.7
	30.2	17.3

CSF MTX and Age



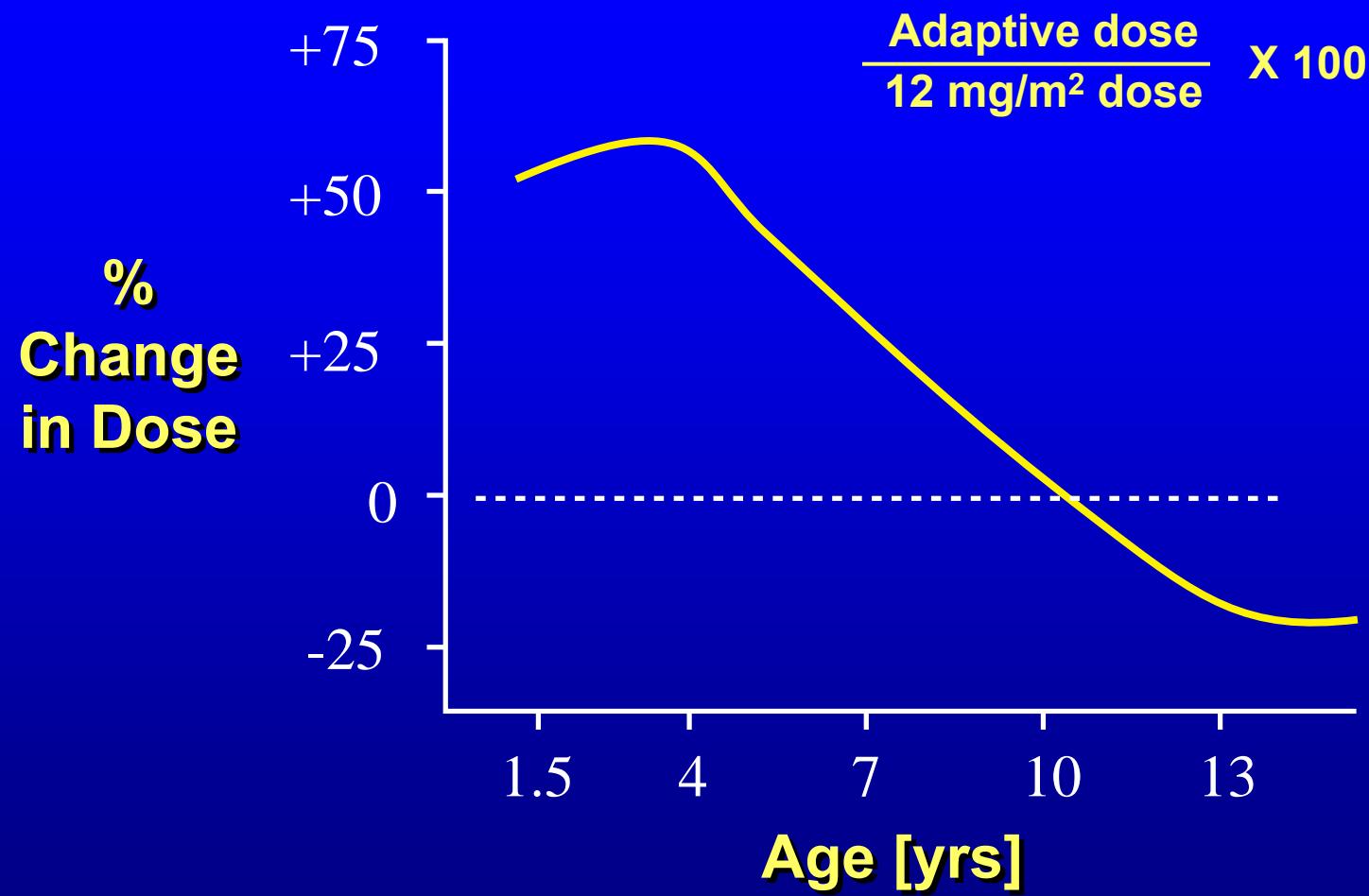
CNS Growth and Development



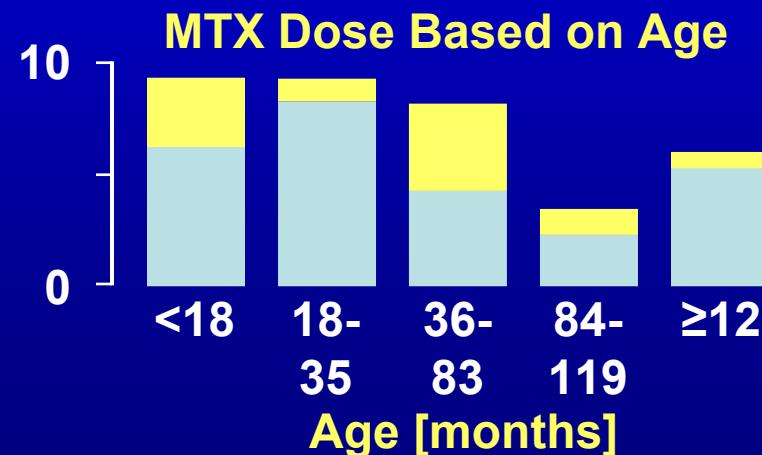
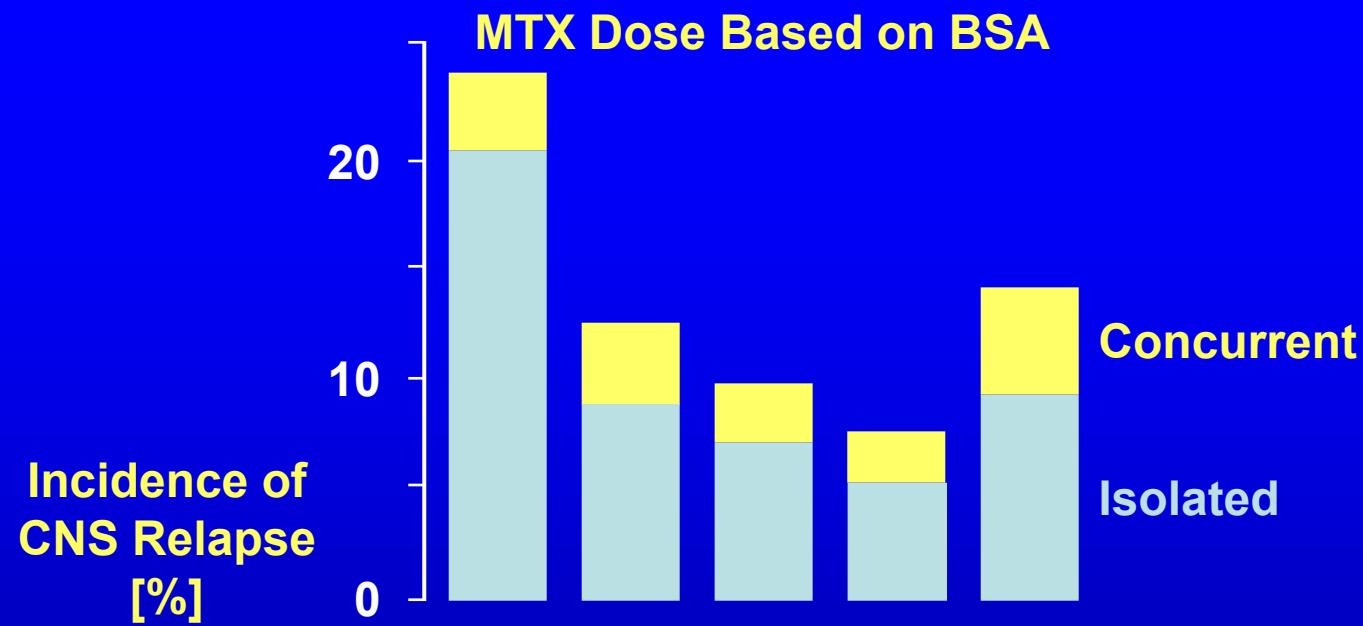
Adaptive IT MTX Dosing Regimen

AGE [YRS]	MTX DOSE [MG]
<1	6
1	8
2	10
³ 3	12

Dose Change with Adaptive Regimen



Effect of Adaptive IT Dosing on Outcome



Dosing Based on Body Surface Area

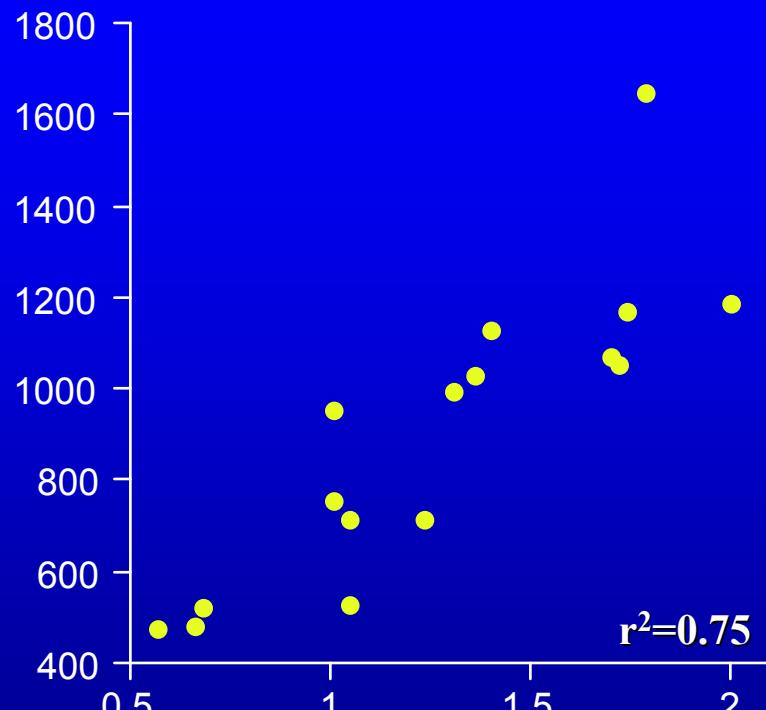
- **BSA = 2-dimensional surface area of the skin**
- **Estimated from formulas using weight & height**
- **Correlation between BSA and kidney/liver function is weak**
- **BSA dosing evolved from scaling doses from animals to humans (toxicology)**

Species	Wt [kg]	BSA [m ²]	Dose [mg]	Dose [mg/kg]	Dose [mg/m ²]
Mouse	0.018	0.0075	0.027	1.5	3.6
Rat	0.25	0.045	0.125	0.5	2.8
Infant	8	0.4	1.25	0.15	3.1
Child	20	0.8	2.5	0.12	3.1
Adult	70	1.85	5.0	0.07	2.7

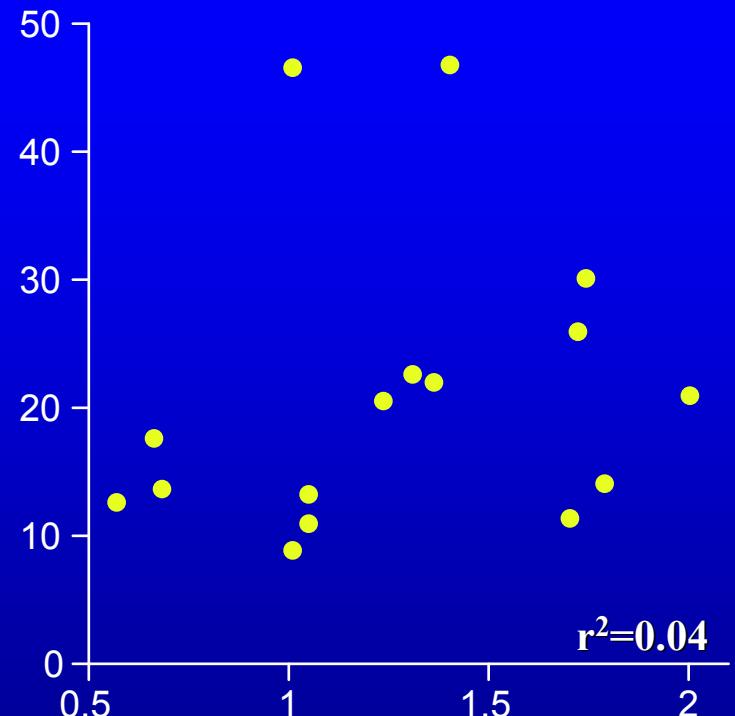
Liver Function (Children)

Liver Vol

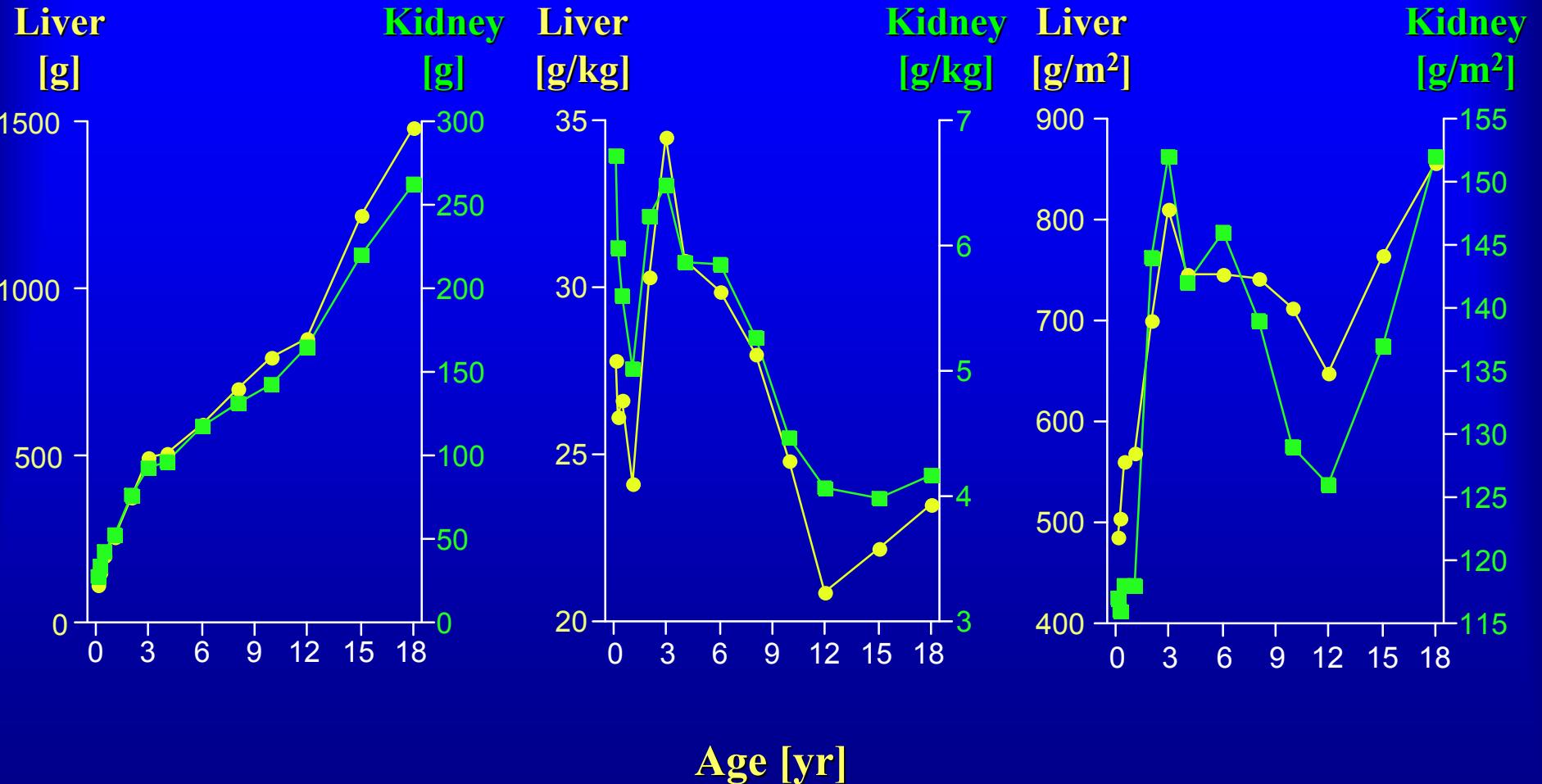
[ml]



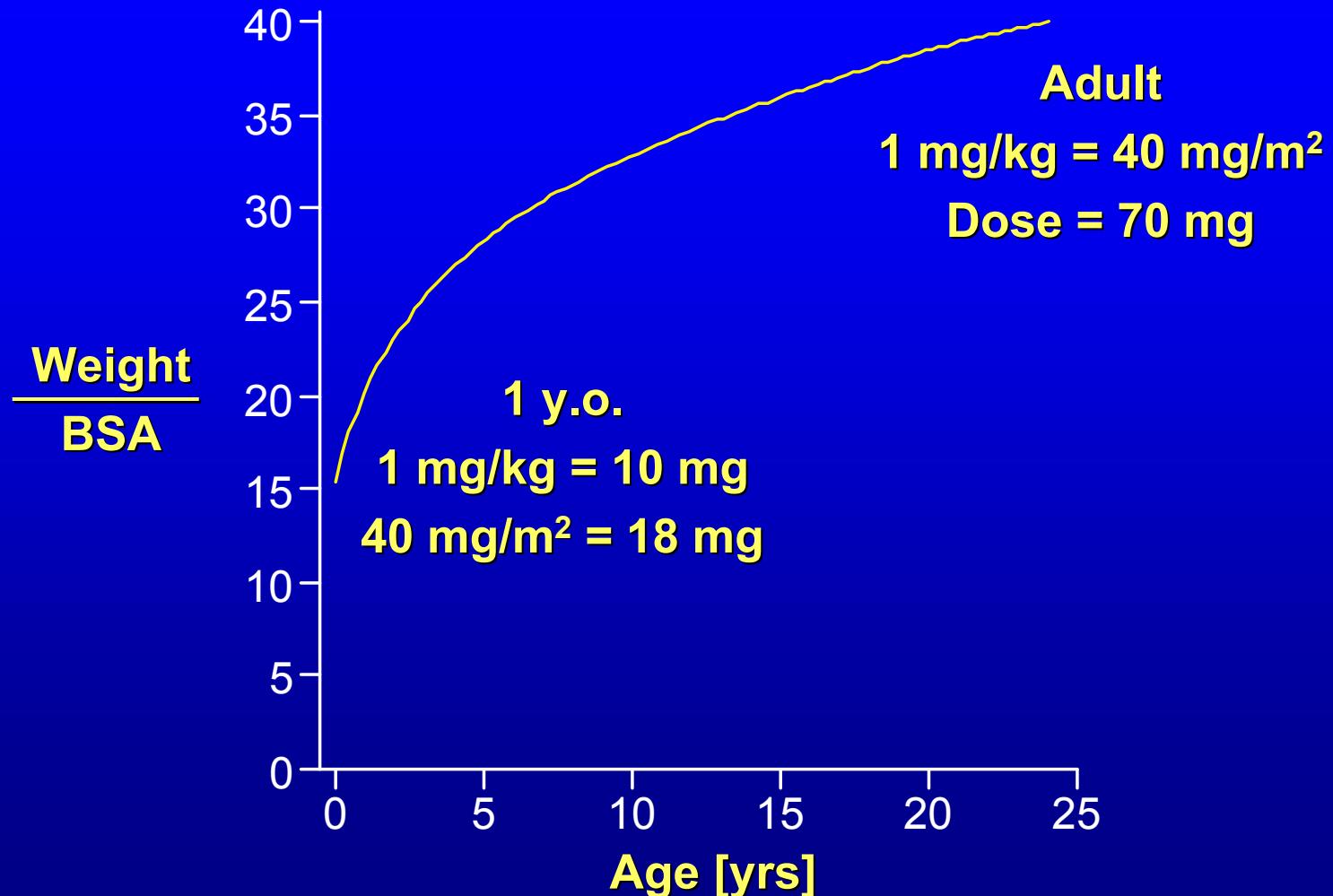
Antipyrine CL
[ml/min]



Excretory Organ Growth



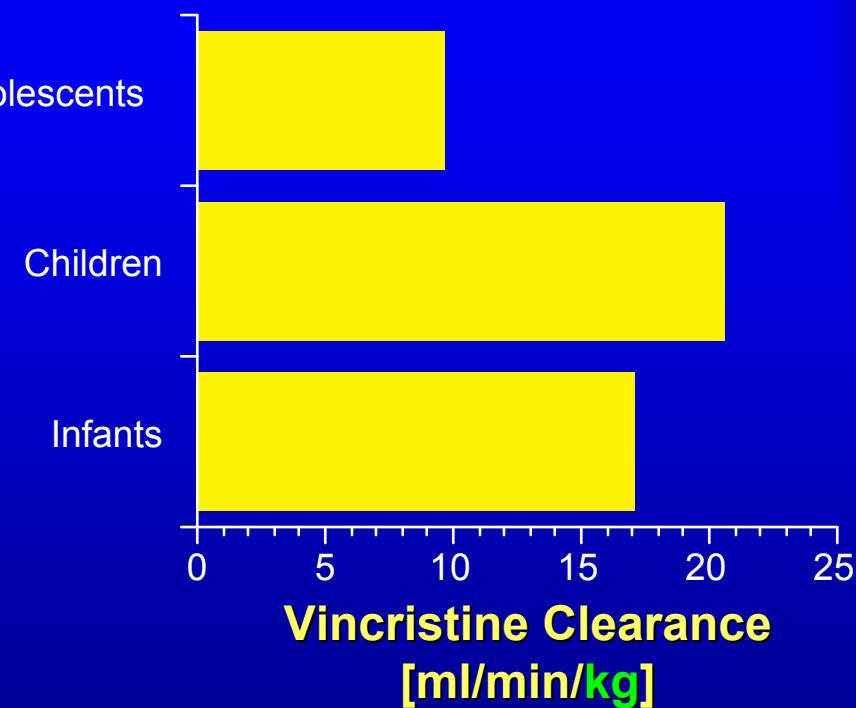
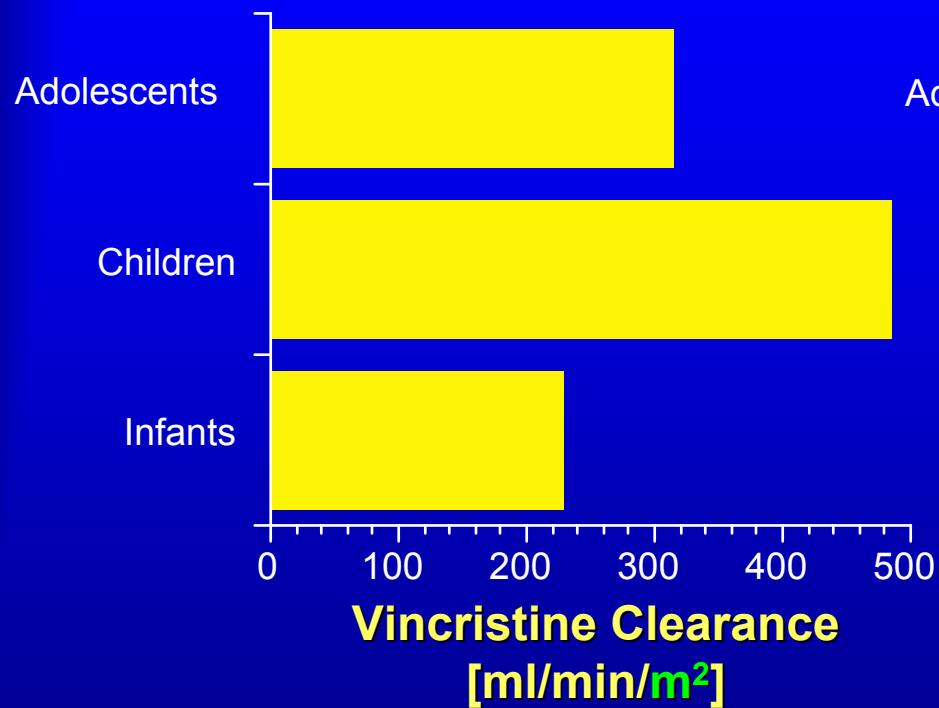
Body Weight:Surface Area



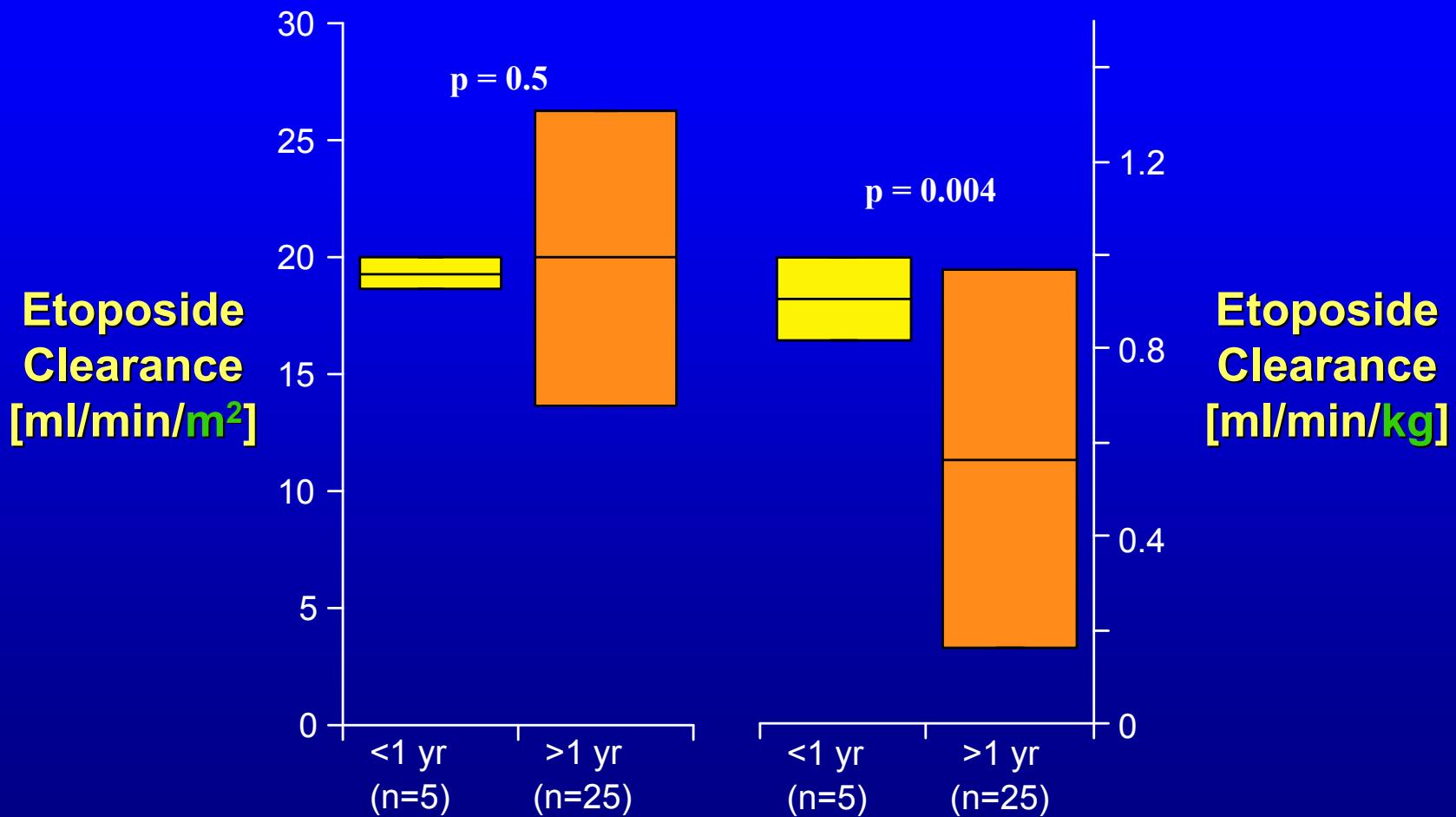
Anticancer Drug Clearance

DRUG	ROUTE OF ELIMINATION	CL _{INFANTS} VS CL _{CHILDREN}	DOSING
Methotrexate	R	↓ (15%)	No adjustments
Mercaptopurine	M	ND	No adjustments
Vincristine	M	↓ (/m ²)	<1 yo, dose/kg
VM26/VP16	M	ND (/m ²)	No adjustments (/m ²)
Doxorubicin	B, M	↓ (/m ²)	<2 yo, dose/kg or ↓ dose/m ²
Cytarabine	M	ND	No adjustment

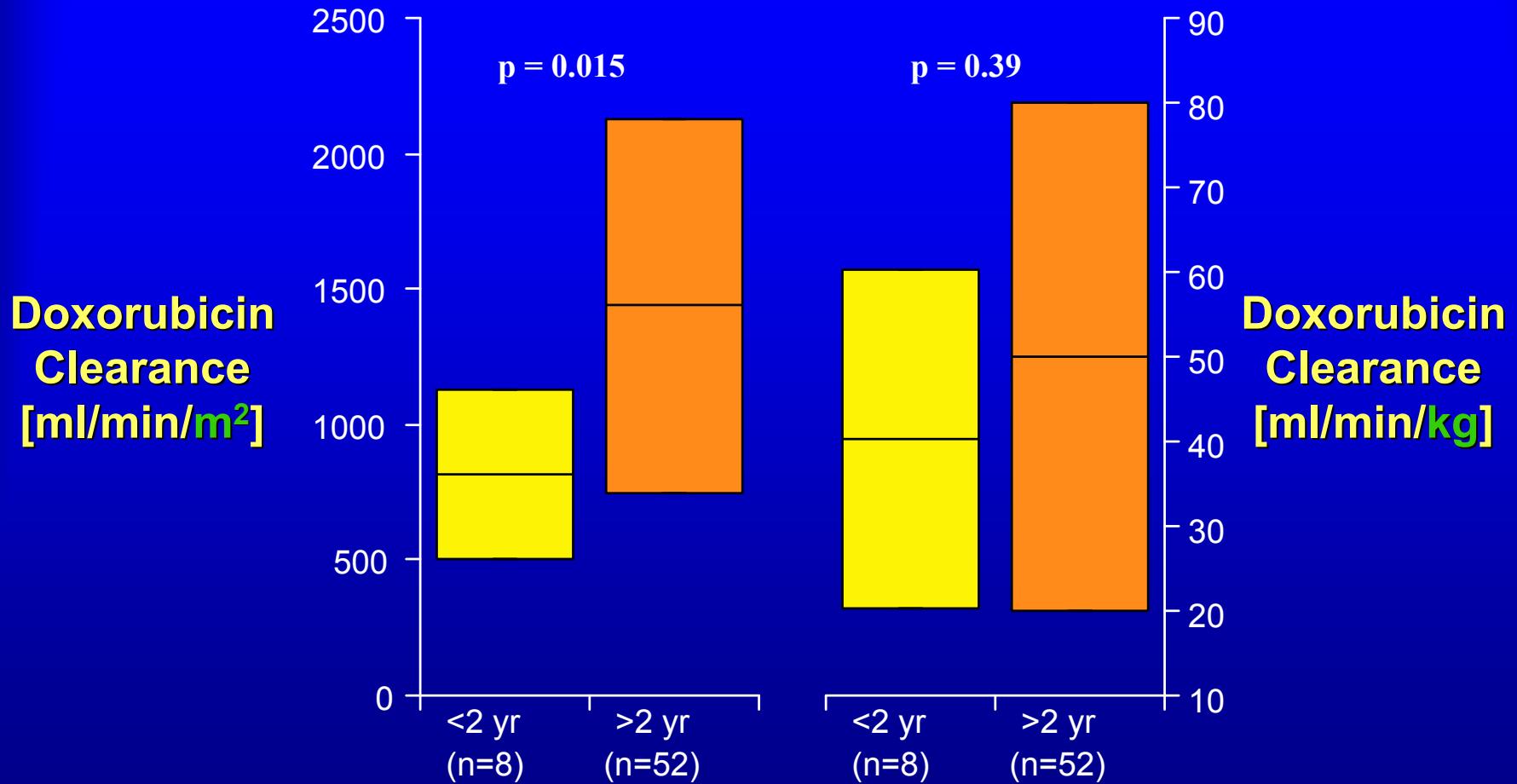
Vincristine Clearance



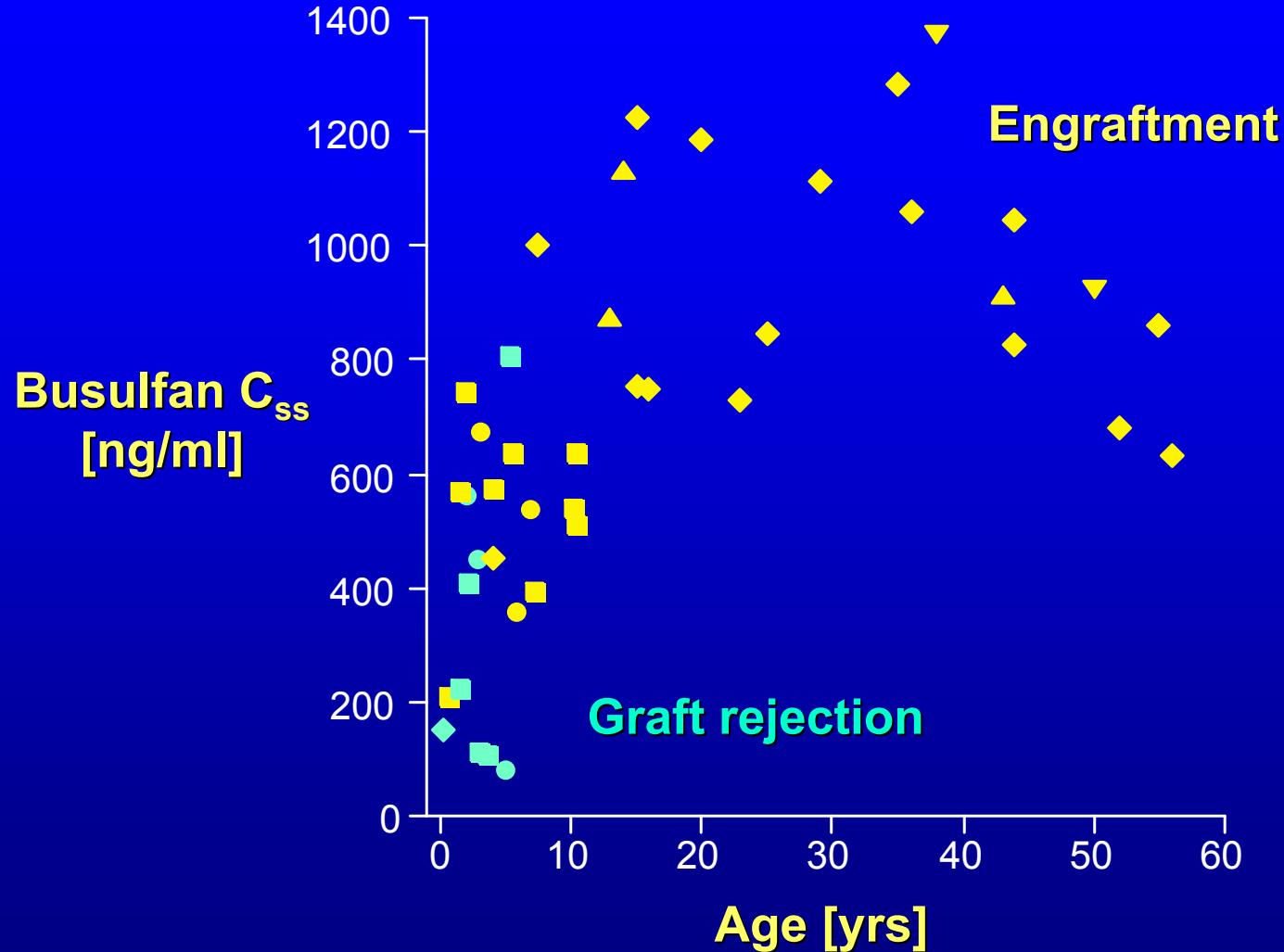
Etoposide Clearance



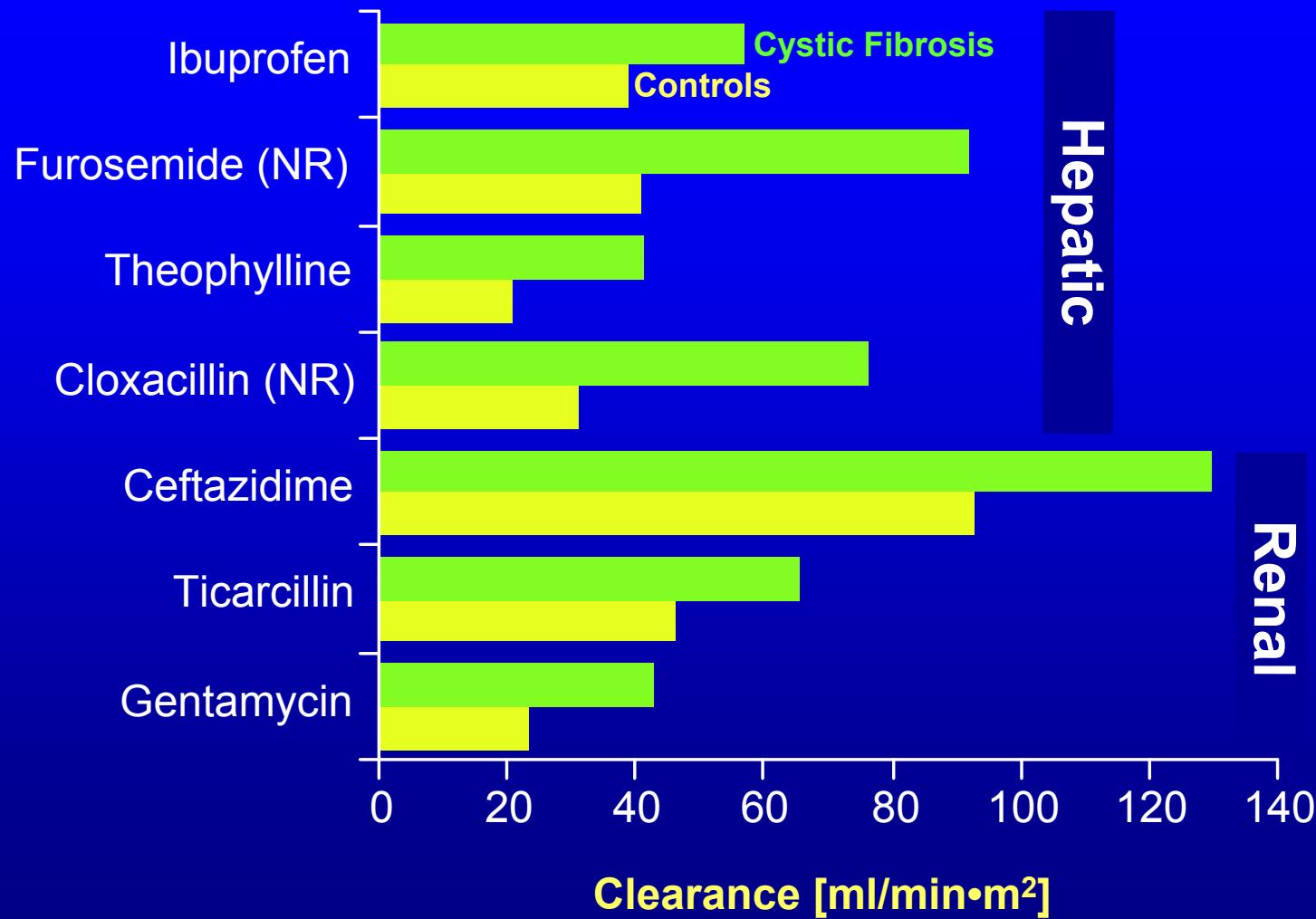
Doxorubicin Clearance



Oral Busulfan (16-30 mg/kg)



Drug Clearance in Cystic Fibrosis



Retinoids

	≤ 12 Yr.	> 12 Yr	Adult
ATRA			
MTD	60 mg/m²/d	90 mg/m²/d	150 mg/m²/d
DLT	Pseudotumor cerebri	HA and PC	Dermatologic
9-cis-RA			
MTD	35 mg/m²/d	85 mg/m²/d	140 mg/m²/d
DLT	Pseudotumor cerebri	HA and PC	HA, diarrhea, dermatologic

Conclusions

- Infants (esp. newborns) may have reduced capacity to eliminate drugs
- Anticipate the effects of ontogeny on drug disposition based on route of elimination
- More systematic pharmacokinetic studies of drugs in infants are needed
- Tissue sensitivity to the toxic effects of drugs may be age-dependent

Cytochrome P450 Enzymes

PRESENT IN FETUS	APPEAR AFTER BIRTH	APPEAR 3-4 MONTHS OF AGE
CYP3A7*	CYP2D6	CYP1A2
CYP1A1	CYP3A4*	
CYP3A5	CYP2C9	
	CYP2C18/19	
	CYP2E1	

* Most abundant form

Gentamicin in the Newborn

